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BULLETIN OF
MATHEMATICAL BIOPHYSICS
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MATHEMATICAL BIOLOGY OF DIVISION OF LABOR BETWEEN TWO INDIVIDUALS OR TWO SOCIAL GROUPS

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The concept of the satisfaction function is applied to the situation in which two individuals may each produce two needed objects of satisfaction, or may each produce only one of the objects and then make a partial exchange. It is shown that with a logarithmic satisfaction function there is no advantage in a division of labor, unless such a division materially increases the purely physical efficiency of production. This result appears to be connected with the particular choice of the form of satisfaction function (logarithmic). While the problem has not been solved for other forms, it is made plausible that satisfaction functions which have an asymptote will lead to a different result.

Next the case is studied in which division of labor occurs between two groups of individuals. It is shown that in this case the relative sizes of the two groups are determined from considerations of maximum satisfaction. Possible applications to problems of urbanization are suggested.

In our two books (Rashevsky, 1948, referred to as HR; 1951, referred to as SB) we have used the concept of the satisfaction function to study problems of motivational interactions between two or more individuals. Other studies in that direction have been made by Anatol Rapoport (1947a, b, c). All the studies were limited to the case in which all individuals engage in the same activity and produce, as a result of it, the same object of satisfaction. The parameters of the satisfaction function were considered as different for different individuals.

In this paper we shall study a few simple instances of a different case—that in which two or more objects of satisfaction are involved. We shall restrict ourselves here to the case of two objects of satisfaction only. As before, we shall assume that the satisfaction function consists of two parts. One varies logarithmically with the amount of the object of satisfaction, and is positive for sufficiently large amounts; the other varies linearly with the amount of work necessary to produce the object of satisfaction, and is always negative. That work is most appropriately measured by the actual energy expenditure. However, we shall measure it here in terms of the time spent on work, which is equivalent to assuming that for different tasks the energy expenditures per unit time are the same. Though this is actually not so, this limitation in no way affects our results.

I

Let x be the amount of one object of satisfaction, and y of another. Let the amounts of time needed to produce x and y be v and w respectively, and let the amounts of objects of satisfaction be proportional to the times (HR, chap. xix; SB, chap. xv). Thus, denoting by a_1 and a_2 two constants, we have

$$x = a_1 v \; ; \qquad y = a_2 w \, . \tag{1}$$

Let an individual be engaged in the production of the first object only. Then (HR, chap. xix; SB, chap. xv), denoting by A_1 and B_1 two other constants, we have for his satisfaction

$$S' = A_1 \log a_1 v - B_1 v \, . \tag{2}$$

This has a maximum for

$$v = \frac{A_1}{B_1} \, . \tag{3}$$

Since the individual adjusts his work so as to maximize his satisfaction, the latter will be

$$S'_m = A_1 \log \frac{A_1 a_1}{B_1} - A_1 \, . \tag{4}$$

If the same individual engages in the production of the second object of satisfaction, then, denoting by A_2 and B_2 two constants, we have

$$S'' = A_2 \log a_2 w - B_2 w \, , \tag{5}$$

which has a maximum for

$$w = \frac{A_2}{B_2} \, , \tag{6}$$

and the maximum value S''_m is

$$S''_m = A_2 \log \frac{A_2 a_2}{B_2} - A_2 \, . \tag{7}$$

The total time which an individual can devote to any work (or, for that matter, the total energy) is limited. Let us denote that maximum value by T. If

$$\frac{A_1}{B_1} + \frac{A_2}{B_2} < T \, , \tag{8}$$

then the individual can engage in the production of both objects of satisfaction, and maximize his satisfactions S' and S'' for both objects independently. He will have an amount $A_1 a_1/B_1$ of the first and an amount $A_2 a_2/B_2$ of the second.

If, however,

$$\frac{A_1}{B_1}+\frac{A_2}{B_2}>T\,, \tag{9}$$

then the individual cannot maximize S' and S'' independently, because v and w are not independent. We now have

$$v+w=T\,. \tag{10}$$

Eliminating w from expression (5) by means of (10), we now find for the total satisfaction

$$S=S'+S''=A_1 \log a_1 v-B_1 v+A_2 \log a_2 (T-v)-B_2 (T-v)\,. \tag{11}$$

Now the individual can adjust his only variable v so as to maximize S by requiring

$$\frac{dS}{dv}=0\,. \tag{12}$$

Introducing (11) into (12), we find

$$A_1 (T-v)-B_1 v (T-v)-A_2 v+B_2 v (T-v)=0\,, \tag{13}$$

which is quadratic in v, and leads to somewhat unwieldy expressions. For simplicity, we shall restrict ourselves to the case $B_1 = B_2 = B$. In other words, we assume that the unpleasantness of both types of work is the same. We then find

$$v=\frac{A_1}{A_1+A_2}T\,. \tag{14}$$

Introducing this into (11), we find for the maximum value S^* of S

$$S^*=A_1 \log \frac{A_1 a_1}{A_1+A_2} T+A_2 \log \frac{A_2 a_2}{A_1+A_2} T-BT\,. \tag{15}$$

If inequality (8) holds, then the maximum total satisfaction S_m is again simply given by the sum of expressions (4) and (7). Thus

$$S_m=A_1 \log \frac{A_1 a_1}{B}+A_2 \log \frac{A_2 a_2}{B}-(A_1+A_2)\,. \tag{16}$$

We now shall prove that

$$S^*<S_m\,. \tag{17}$$

Introducing (15) and (16) into (17) and rearranging, we see that the latter is equivalent to

$$(A_1+A_2)\log B+(A_1+A_2)<(A_1+A_2)\log\frac{A_1+A_2}{T}+BT\,. \quad (18)$$

After further rearrangements, inequality (18) may be brought into the form

$$\log\frac{BT}{A_1+A_2}<\frac{BT}{A_1+A_2}-1\,. \quad (19)$$

Put

$$1-\frac{BT}{A_1+A_2}=z\,. \quad (20)$$

But S^* has a meaning only if (9) holds. This implies that

$$0<z<1\,. \quad (21)$$

Inequality (19) now becomes

$$\log(1-z)<-z\,. \quad (22)$$

That this inequality always holds is seen from the fact that the expansion of log $(1-z)$ consists of only negative terms, the first being $-z$. This proves inequality (17), which is also intuitively evident.

Now consider two individuals, each in the position described above, that is, each producing both objects of satisfaction under the condition expressed by inequality (9). However, while (9) holds, let

$$\frac{A_1}{B}<T \quad \text{and} \quad \frac{A_2}{B}<T\,. \quad (23)$$

We may now ask whether the two individuals will gain anything by dividing their labor, that is, one of them producing only the first object of satisfaction, the other the second, and then sharing their results in an appropriate manner.

Let the first individual produce only the first object of satisfaction in an amount x_0, while spending the time v_0; the second individual produce only the second object of satisfaction in the amount y_0, spending the time w_0. Then let them divide the results so that the first will have x_1 and y_1 of both objects, the second x_2 and y_2. Thus

$$x_1+x_2=x_0\,; \quad (24)$$

$$y_1+y_2=y_0\,. \quad (25)$$

Since the first individual works only to produce the first object of satisfaction in the amount x_0, therefore, the negative part of his satisfaction function will always be $Bv_0 = Bx_0/a_1$, regardless of the method of sharing. Similarly, the negative part of the satisfaction function of the second individual will be $Bw_0 = By_0/a_2$. The total satisfaction functions will be, respectively,

$$S_1 = A_1 \log x_1 + A_2 \log y_1 - \frac{B}{a_1} x_0 ; \tag{26}$$

$$S_2 = A_1 \log x_2 + A_2 \log y_2 - \frac{B}{a_2} y_0 . \tag{27}$$

How will the quantities x_1, x_2, y_1, and y_2 be determined? This problem of "trading" one object for another, between two individuals, when each tries to obtain the best advantage from the trading, has been solved for two individuals and two objects by G. Evans (1930, pp. 125–28). A more general case, for any number of individuals and any number of objects, has been treated by the present author (1952a). The reader is referred for details to the two sources mentioned above, where the proof of the following is given.

We form the expressions

$$X_1 = \frac{\partial S_1}{\partial x_1} ; \qquad Y_1 = \frac{\partial S_1}{\partial y_1} ; \qquad X_2 = \frac{\partial S_2}{\partial x_2} ; \qquad Y_2 = \frac{\partial S_2}{\partial y_2} . \tag{28}$$

We then have in the present case

$$\frac{X_1(x_1, y_1)}{X_2(x_0 - x_1, y_0 - y_1)} = \frac{Y_1(x_1, y_1)}{Y_2(x_0 - x_1, y_0 - y_1)} , \tag{29}$$

and

$$\frac{y_1}{x_1 - x_0} = - \frac{X_1(x_1, y_0)}{Y_1(x_1, y_1)} . \tag{30}$$

Equations (29) and (30), together with (24) and (25), determine the four unknown quantities, x_1, x_2, y_1, and y_2.

From (26) and (27) we have

$$X_1 = \frac{A_1}{x_1} ; \qquad X_2 = \frac{A_1}{x_2} ; \qquad Y_1 = \frac{A_2}{y_1} ; \qquad Y_2 = \frac{A_2}{y_2} . \tag{31}$$

Introducing this into (29) we obtain, after rearrangements,

$$\frac{x_0}{x_1} = \frac{y_0}{y_1} . \tag{32}$$

Introducing (31) into (30), we find

$$\frac{1}{x_1 - x_0} = - \frac{A_1}{A_2 x_1} . \tag{33}$$

Equations (24), (25), (32), and (33) give

$$\left.\begin{aligned} x_1 &= \frac{A_1}{A_1+A_2}\,x_0\,; \qquad & x_2 &= \frac{A_2}{A_1+A_2}\,x_0\,; \\ y_1 &= \frac{A_1}{A_1+A_2}\,y_0\,; \qquad & y_2 &= \frac{A_2}{A_1+A_2}\,y_0\,. \end{aligned}\right\} \tag{34}$$

Introducing these values into (26) and (27), we find

$$S_1 = A_1 \log \frac{A_1 x_0}{A_1+A_2} + A_2 \log \frac{A_1 y_0}{A_1+A_2} - \frac{B}{a_1}\,x_0\,; \tag{35}$$

$$S_2 = A_1 \log \frac{A_2 x_0}{A_1+A_2} + A_2 \log \frac{A_2 y_0}{A_1+A_2} - \frac{B}{a_2}\,y_0\,. \tag{36}$$

The amounts x_0 and y_0 are still left indefinite. Expressions (35) and (36) specify S_1 and S_2 for any given values of x_0 and y_0. These will be determined by the two individuals. If they act egoistically, or individualistically, then the first individual will choose his x_0 so as to maximize S_1, while the second will choose such a y_0 as to maximize S_2. In other words, x_0 and y_0 are in this case determined by

$$\frac{\partial S_1}{\partial x_0} = 0\,; \qquad \frac{\partial S_2}{\partial y_0} = 0\,. \tag{37}$$

Equations (37), together with (35) and (36), give

$$x_0 = \frac{A_1 a_1}{B}\,; \qquad y_0 = \frac{A_2 a_2}{B}\,, \tag{38}$$

which are the same as would be obtained from (3) and (6), for the case of a single individual working under conditions (8). Introducing (38) into (35) and (36), we obtain

$$S_{1m} = A_1 \log \frac{A_1^2 a_1}{B\,(A_1+A_2)} + A_2 \log \frac{A_1 A_2 a_2}{B\,(A_1+A_2)} - A_1\,; \tag{39}$$

$$S_{2m} = A_1 \log \frac{A_1 A_2 a_1}{B\,(A_1+A_2)} + A_2 \log \frac{A_2^2 a_2}{B\,(A_1+A_2)} - A_2\,. \tag{40}$$

In order to see whether the two individuals gain anything from the division of labor, we must compare S_{1m} and S_{2m} with S^* as given by (15). We have, from (15) and (39),

$$S_{1m} - S^* = (A_1+A_2) \log \frac{A_1}{BT} + (BT - A_1)\,. \tag{41}$$

Put

$$\frac{BT - A_1}{BT} = z\,. \tag{42}$$

Because of (9) and (23)

$$0 < z < 1 .$$

Now (41) may be written

$$S_{1m} - S^* = (A_1 + A_2) \log (1 - z) + BTz . \qquad (43)$$

Expanding log $(1 - z)$, we find

$$S_{1m} - S^* = [BT - (A_1 + A_2)] \, z + \text{negative terms in } z . \qquad (44)$$

Hence

$$S_{1m} - S^* < 0 . \qquad (45)$$

Similarly, we prove that

$$S_{2m} - S^* < 0 . \qquad (46)$$

Thus in the case of egoistic behavior, the division of labor does not lead to any advantage, with the assumptions made above.

If both individuals exhibit altruistic or collectivistic behavior, they will determine x_0 and y_0 from

$$\frac{\partial (S_1 + S_2)}{\partial x_0} = 0 ; \qquad \frac{\partial (S_1 + S_2)}{\partial y_0} = 0 . \qquad (47)$$

Introducing (35) and (36) into (47), we now find

$$x_0 = \frac{2 A_1 a_1}{B} ; \qquad y_0 = \frac{2 A_2 a_2}{B} . \qquad (48)$$

Introducing (48) into (35) and (36), we obtain corresponding expressions for S_{1m} and S_{2m}, which now differ from (39) and (40) by $(A_1 + A_2)$ log 2. Therefore, instead of (44), we now find

$$S_{1m} - S^* = (A_1 + A_2) \log 2 (1 - z) + BTz . \qquad (49)$$

If $z < \frac{1}{2}$, that is, if

$$\frac{A_1}{B} > \frac{1}{2} T , \qquad (50)$$

then $S_{1m} - S^* > 0$. It will, however, be positive even for values of z which are not too much smaller than $\frac{1}{2}$, for then the positive term BTz in (49) will still prevail. Thus for altruistic behavior $S_{1m} > S^*$ if (50) holds, and, similarly, $S_{2m} > S^*$ if

$$\frac{A_2}{B} > \frac{1}{2} T . \qquad (51)$$

We notice that at least one of the two inequalities (50) and (51) must hold, if (9) holds, with $B_1 = B_2 = B$. Hence, for altruistic behavior, division of labor leads to an advantage for at least one of the two individuals.

The important question is whether the above conclusions are due to the specific choice of the logarithmic function for the satisfaction. That choice leads to the following peculiarity.

If an individual produces an object of satisfaction, but has to give part of it away, retaining only a fraction x_1, then his satisfaction function is given by

$$S = A \log \alpha x - \frac{B}{a} x . \tag{52}$$

This has a maximum for

$$x = \frac{A a}{B} , \tag{53}$$

which is independent of α. With such a satisfaction function, an individual who has to share the results of his activity does not increase the activity. This results in a certain loss of advantage in sharing. If we put

$$S = A \log (1 + \alpha x) - \frac{B}{a} x , \tag{54}$$

then the optimum value of x is

$$x = \frac{A a}{B} - \frac{1}{\alpha} . \tag{55}$$

In this case an individual will work the less, the more he has to share. A similar situation is obtained if we put

$$S = A \sqrt{\alpha x} - \frac{B}{a} x . \tag{56}$$

Such a situation is in no way implausible. With other satisfaction functions, the situation may be different. For example, put

$$S = 1 - e^{-A\alpha x} - \frac{B}{a} x . \tag{57}$$

The value of x which maximizes (57) is

$$x = \frac{1}{A \alpha} \log \frac{A a \alpha}{B} . \tag{58}$$

For $\alpha = 1$, when the individual retains all he makes, the maximum value x' of x is

$$x' = \frac{1}{A} \log \frac{A a}{B} . \tag{59}$$

In order that a maximum exists at all *in both cases*, it is necessary that

$$A a > B \qquad \text{and} \qquad \alpha > \frac{B}{A a} . \tag{60}$$

From (58) and (59) we see that $x > x'$ implies

$$(1-\alpha)\log\frac{Aa}{B} > -\log\alpha\,. \tag{61}$$

For $\alpha = 0$, the value of $-\log\alpha$ is positive infinite; for $\alpha = 1$, it is zero, and the slope of the $-\log\alpha$ curve at $\alpha = 1$ is equal to 1 (Fig. 1).

The straight line $(1-\alpha)\log Aa/B$ is tangent to the line $-\log\alpha$ if $\log(Aa/B) = 1$, or $Aa/B = e$ (Fig. 1, broken line). In that case inequality (61) does not hold, and hence $x' > x$. If, however, $\log Aa/B > 1$, or

$$\frac{Aa}{B} > e\,, \tag{62}$$

then in the interval between $\alpha = \alpha_1$ and $\alpha = 1$ (Fig. 1, full line) inequality (61) holds, and $x > x'$. The stronger inequality (62), the smaller the value of α_1. Hence, if (62) holds, an individual who retains only a fraction α of what he produces will produce somewhat more than if he retains everything, provided α does not fall below a critical value α_1. That critical value decreases with increasing "efficiency" a, and with decreasing difficulty B of the work. If $\alpha < \alpha_1$, then the individual produces less than if he retains everything. If $\alpha < B/Aa$ [cf. (60)], then the individual will not work at all.

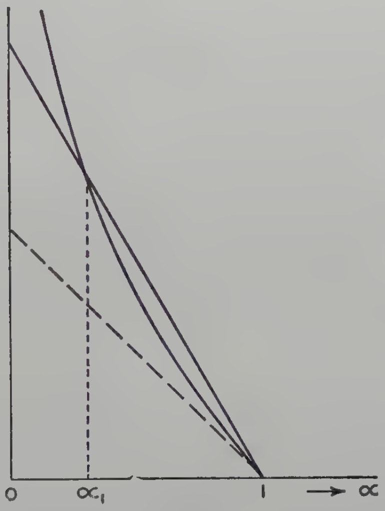

FIGURE 1

It would be interesting to investigate the problem of division of labor with a satisfaction function of the form (57). Unfortunately, this leads to quite unwieldly expressions and transcendental equations. We shall, therefore, not investigate this problem now. Instead we shall make the important remark that very plausible conditions which affect the satisfaction function indirectly may result in an advantage of a division of labor for both individuals, even for egoistic behavior. An attempt by an individual to engage in two different tasks is likely to result in a decrease of efficiency of each task. This may be due to the necessity of special training in the particular task, or to the waste of time involved in switching over from one task to another. As a result of this, the values a_1 and a_2 in expressions (39) and (50), which correspond to a division of labor, are likely to be much larger than the values of those quantities in expression (15) for S^*. We shall denote those latter values by a_1^* and a_2^*.

Instead of (41) we now have

$$S_{1m} - S^* = (A_1 + A_2) \log \frac{A_1}{BT} + (BT - A_1) + A_1 \log \frac{a_1}{a_1^*} + A_2 \log \frac{a_2}{a_2^*}. \tag{63}$$

As we have seen above, the sum of the first two terms is always negative. If, however,

$$a_1 \gg a_1^* ; \qquad a_2 \gg a_2^* , \tag{64}$$

then, if the last two inequalities are sufficiently strong, the last two positive terms in (63) will prevail over the negative terms, and $S_{1m} - S^*$ will be positive. The same holds for $S_{2m} - S^*$. A division of labor may thus be of advantage to both individuals for purely physical, rather than psychobiological, reasons.

II

We now shall discuss the problem of division of labor not between two individuals, but between two social groups.

Let the total population N_0 of a society be divided into two groups, containing N_1 and N_2 individuals, correspondingly. Let the individuals of the first group engage in the production of the first object of satisfaction, producing a total amount x_0 for the group. Similarly, let all individuals of the second group engage in the production of the second object of satisfaction only, producing a total of y_0. After a trading or exchange, such as discussed above, the *groups* will possess amounts x_1, x_2, y_1, and y_2. For simplicity, we shall assume that the satisfaction functions of all the individuals are the same, and that *within a group* the amounts are divided equally. Therefore, an individual of the first group will possess amounts x_1/N_1, y_1/N_1, and will produce x_0/N_1. An individual of the second group will possess amounts x_2/N_2, y_2/N_2 and produce y_0/N_2. Denoting now the satisfaction functions of each individual by s_1 and s_2, correspondingly, we have

$$s_1 = A_1 \log \frac{x_1}{N_1} + A_2 \log \frac{y_1}{N_1} - \frac{B}{a_1}\frac{x_0}{N_1}; \tag{65}$$

$$s_2 = A_1 \log \frac{x_2}{N_2} + A_2 \log \frac{y_2}{N_2} - \frac{B}{a_2}\frac{y_0}{N_2}. \tag{66}$$

The total satisfactions of each group are given by

$$S_1 = N_1 s_1 = N_1 A_1 \log \frac{x_1}{N_1} + N_1 A_2 \log \frac{y_1}{N_1} - \frac{B}{a_1} x_0; \tag{67}$$

$$S_2 = N_2 s_2 = N_2 A_1 \log \frac{x_2}{N_2} + N_2 A_2 \log \frac{y_2}{N_2} - \frac{B}{a_2} y_0. \tag{68}$$

To determine x_1, x_2, y_1 and y_2, we use the same procedure as before. For egoistic behavior we then obtain the following values for the optimum satisfactions after the exchange:

$$S_{1m} = N_1 A_1 \log \frac{A_1^2 a_1}{B(A_1 + A_2)} + N_1 A_2 \log \frac{A_1 A_2 a_2}{B(A_1 + A_2)} \frac{N_2}{N_1} - N_1 A_1; \tag{69}$$

$$S_{2m} = N_2 A_1 \log \frac{A_1 A_2 a_1}{B(A_1 + A_2)} \frac{N_1}{N_2} + N_2 A_2 \log \frac{A_2^2 a_2}{B(A_1 + A_2)} - N_2 A_2. \tag{70}$$

For $N_1 = N_2 = 1$ these expressions reduce to expressions (39) and (40), as should be the case.

The satisfactions per individual after exchange are:

$$s_{1m} = A_1 \log \frac{A_1^2 a_1}{B(A_1 + A_2)} + A_2 \log \frac{A_1 A_2 a_2}{B(A_1 + A_2)} \frac{N_2}{N_1} - A_1; \tag{71}$$

$$s_{2m} = A_1 \log \frac{A_1 A_2 a_1}{B(A_1 + A_2)} \frac{N_1}{N_2} + A_2 \log \frac{A_2^2 a_2}{B(A_1 + A_2)}. \tag{72}$$

As we see, both s_1 and s_2 depend on N_1/N_2. What determines that ratio?

For $N_1/N_2 = 0$, we have $s_{2m} < s_{1m}$; for $N_1/N_2 = \infty$, $s_{2m} > s_{1m}$. Hence there is a value of N_1/N_2 for which $s_{1m} = s_{2m}$. If N_1/N_2 is less than that value, then $s_{1m} > s_{2m}$, and the individuals of the second group will leave that group and join the first group, in order to increase their satisfaction. The reverse holds true if N_1/N_2 is larger than the value for which $s_{1m} = s_{2m}$. Hence N_1/N_2 will be maintained at that value, which makes $s_{1m} = s_{2m}$.

Putting

$$\frac{N_1}{N_0} = \eta; \qquad \frac{N_1}{N_2} = \frac{\eta}{1-\eta}, \tag{73}$$

equating the right sides of (71) and (72), and rearranging, we find:

$$\left(\frac{A_1}{A_2}+1\right)\log\frac{A_1}{A_2}-\left(\frac{A_1}{A_2}-1\right)=\left(\frac{A_1}{A_2}+1\right)\log\frac{\eta}{1-\eta}. \tag{74}$$

This gives

$$\frac{\eta}{1-\eta}=\frac{A_1}{A_2}\,e^{-(A_1-A_2)/(A_1+A_2)}. \tag{75}$$

From (75) we find

$$\eta=\frac{\dfrac{A_1}{A_2}\quad e^{-(A_1-A_2)/(A_1+A_2)}}{1+\dfrac{A_1}{A_2}e^{-(A_1-A_2)/(A_1+A_2)}}. \tag{76}$$

As $A_1/A_2 \to \infty$, $\eta \to 1$. The greater the satisfaction from the results of a given activity, the more individuals will choose that activity.

It seems somewhat surprising that neither B nor a_1 and a_2 enter into the expression for η. This is due to the particular choice of the satisfaction function. Exact solutions with other types of functions are very cumbersome. We may, however, give an example of a limiting case.

Let the satisfaction due to the possession of an amount x of the first object of satisfaction be given by

$$A_1\log(1+x), \tag{77}$$

while for the second object let the satisfaction increase linearly, and be given by A_2y. If

$$A_2>\frac{B}{a_2}, \tag{78}$$

then an individual producing only the second object will put in all the available time T. If inequality (78) is reversed, he will not work at all.

With these assumptions we find for the satisfaction functions s_1 and s_2

$$s_1=A_1\log\left(1+\frac{x_1}{N_1}\right)+A_2\frac{y_1}{N_1}-\frac{B}{a_1}\frac{x_0}{N_1}; \tag{79}$$

$$s_2=A_1\log\left(1+\frac{x_2}{N_2}\right)+A_2\frac{y_2}{N_2}-\frac{B}{a_2}\frac{y_0}{N_2}. \tag{80}$$

By multiplying s_1 and s_2 by N_1 and N_2, respectively, we find the satisfactions for each group as a whole.

Now using the same procedure as before, which led to equations (34), (35), and (36), we find

$$x_1=\eta x_0;\qquad x_2=(1-\eta)x_0; \tag{81}$$

$$y_1=\frac{A_1N_0x_0(1-\eta)}{A_2(N_0+x_0)};\qquad y_2=y_0-\frac{A_1N_0x_0(1-\eta)}{A_2(N_0+x_0)}; \tag{82}$$

so that the total satisfactions for each group are:

$$S_1 = N_1 A_1 \log\left(1 + \frac{x_0}{N_0}\right) + \frac{A_1 N_0 x_0 (1-\eta)}{N_0 + x_0} - \frac{B}{a_1} x_0 ; \tag{83}$$

$$S_2 = N_2 A_1 \log\left(1 + \frac{x_0}{N_0}\right) + A_2 y_0 - \frac{A_1 N_0 x_0 (1-\eta)}{N_0 + x_0} - \frac{B}{a_2} y_0 . \tag{84}$$

We recall now that x_0 is determined by

$$\frac{\partial S_1}{\partial x_0} = 0 , \tag{85}$$

whereas

$$y_0 = T . \tag{86}$$

Introducing (83) into (85), we find:

$$N_0 + x_0 = \frac{\eta N_0 A_1 a_1 + N_0 \sqrt{\eta^2 A_1^2 a_1^2 + 4 A_1 a_1 B (1-\eta)}}{2B} . \tag{87}$$

The other root, being negative, has no physical meaning. Since we are dealing here only with an illustration, we shall simplify expression (87) considerably by considering the case in which B is so small that the term in B under the radical can be dropped. This implies not too small an η. We must have

$$B_1 \ll \frac{\eta^2 A_1 a_1}{4} . \tag{88}$$

With this assumption, we find:

$$x_0 = \frac{N_0 A_1 a_1 \eta}{B} . \tag{89}$$

Now introducing (86) and (89) into (83) and (84), and dividing the latter two by N_1 and N_2, correspondingly, we find

$$s_{1m} = A_1 \log \frac{A_1 a_1 \eta}{B} + A_1 \frac{1-\eta}{\eta} - A_1 ; \tag{90}$$

$$s_{2m} = A_1 \log \frac{A_1 a_1 \eta}{B} + \frac{A_2 T}{(1-\eta) N_0} - A_1 - \frac{BT}{a_2 (1-\eta) N_0} . \tag{91}$$

Again η is determined by equating s_{1m} and s_{2m}. This leads to the following equation

$$\frac{A_1}{A_2} \frac{1-\eta}{\eta} - \frac{T}{(1-\eta) N_0} + \frac{BT}{A_2 a_2 (1-\eta) N_0} = 0 . \tag{92}$$

Put

$$\frac{A_1}{A_2} = \nu ; \qquad \frac{T}{N_0} = \alpha ; \qquad \frac{B}{A_2 a_2} = \beta' ; \qquad \beta = 1 - \beta' ; \tag{93}$$

and again assume B so small that

$$\beta' < 1 ; \quad \beta > 0 . \tag{94}$$

Equation (92) now gives

$$\eta = \frac{2\nu + \alpha\beta - \sqrt{\alpha^2\beta^2 + 4\alpha\beta\nu}}{2\nu} . \tag{95}$$

The other root is discarded as giving $\eta > 1$.

As $\nu = A_1/A_2 \rightarrow \infty$, $\eta \rightarrow 1$. This is seen by writing (95) as follows:

$$\nu = 1 + \frac{\alpha\beta}{2\nu} - \frac{\alpha\beta}{2\nu}\sqrt{1 + \frac{4\nu}{\alpha\beta}} . \tag{96}$$

For very large values of ν this becomes

$$\eta = 1 - \sqrt{\frac{\alpha\beta}{\nu}} . \tag{97}$$

Because of (93) this gives:

$$\eta = 1 - \sqrt{\frac{T(A_2 a_2 - B)}{N_0 A_1 a_2}} . \tag{98}$$

Now η does contain A_2, as well as B_1, N_0, and a_2. The larger N_0, the total population, the more rapidly η approaches unity.

III

The results of the preceding section may be applied to the problem of the ratio of urban to rural population. Actually, both urban and rural populations each engage in a number of different activities. As a first rough approximation we may lump these activities in two categories: agricultural and urban. The first produces mainly food. The second produces other necessities, such as clothing, tools, etc. The ratio A_1/A_2 measures the relative importance of the two. In early history the relative importance of food was most pronounced, A_1/A_2 was very large, and most of the population was agricultural. The ratio A_1/A_2, in general, also depends on climatic conditions. In a warm climate the need for such city products as clothing is much less than in a cold climate. Thus the ratio $1 - \eta$ of the urban to total population is also affected by climatic conditions at those early stages.

As we have seen elsewhere (Rashevsky, 1952b) the value $1 - \eta$ determines the rate of technological development. The increase in technology increases the value A_2. For example, in a modern society the need, even in the country, for such urban products as refrigerators, radios, etc. is very great. Thus technological development, which increases with $\eta' = 1 - \eta$, favors in its turn the increase of η'.

Further study of these problems will be of importance for the dynamics of historical processes.

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A MATHEMATICAL THEORY OF CAPILLARY EXCHANGE AS A FUNCTION OF TISSUE STRUCTURE

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A mathematical theory of the process of the exchange of substances between the blood in the capillaries of a homogeneous tissue and the extracellular space, and between the extracellular space and the cells is developed. An ideal geometry of the tissue is assumed, based to some extent on recent anatomical work concerning the functional distinction between two types of capillaries, the arteriolo-venular and the true capillaries. Equations are developed relating the concentration in the arterial blood to the mean capillary concentration, the concentration at the wall of the capillary in the extracellular space, and the average concentration in the extracellular space, and also relating the cellular concentration to the average extracellular concentration. The solutions of the equations are given for certain special cases and numerical results obtained. It is shown that the average extracellular concentration is a sensitive function of the permeability of the capillary wall and also is strongly influenced by the diffusion coefficient of the extracellular space. Furthermore, it is shown that the speed with which the average extracellular concentration approaches the steady state is largely a function of the permeability of the capillary wall.

I. Introduction. Most cells of organisms with closed circulatory systems must depend upon the system to bring to their local environments materials necessary for their maintenance and to remove their diffusible products from such environments. Since most cells are separated from the blood and lymph capillaries by a connective tissue matrix (Gersh, 1952), the efficiency of the supply and removal of substances (for any given arrangement of the capillaries) must depend partially on the characteristics of the ground substance of the connective tissue, and upon the amount of substance through which diffusion may occur, relative to the amount of fibrous and other material which is inert with respect to diffusion.

The aim of the present work is to analyze the influence of the interstitial matrix and capillary permeability upon the exchange of substances between the cells and the blood. Many approximations and idealizations seem necessary to obtain results which may be compared with experiment.

However, as N. Rashevsky (1948) has pointed out in another connection, even if we knew exactly the geometry of a given tissue and knew precisely the blood flows, diffusion coefficients, etc. necessary for the calculation of the exchange relations, and could solve the exceedingly complex boundary value problem so presented, the results would still be of limited usefulness. This is true because the geometry, etc. of the solved problem would be special cases of an almost unlimited number of possible geometries. The analysis which is developed here assumes as known certain tissue parameters and certain data concerning blood flow in the capillaries, which are known only inexactly, or not at all. However, these data seem necessary for a detailed study of the exchange relations and are definitely data which could be obtained by experiment. The need for such data may stimulate work aimed at obtaining them. But, even in the absence of exact measurements, certain relations become evident and certain tentative conclusions may be drawn.

In the following, a brief discussion is given of the labile character of the tissues and of the extracellular matrix, then blood-tissue fluid exchange is described. Next, consideration is given to some experimental and theoretical work on blood-tissue molecular exchange. This is followed by a consideration of the anatomy of the capillary bed. On the basis of the previous discussion, a tissue model is then presented and equations governing the blood-tissue exchanges are formulated. Some applications of the solutions are considered, and a discussion of various implications of the results is given.

II. The extracellular matrix and tissue changes. I. Gersh (1952) has recently discussed the characteristics of the ground substance of the connective tissue. The ground substance is shown to be labile, and its plasticity is related in some cases to the action of certain connective tissue cells. Changes in the ground substance organization are shown to be related to tumor growth, regeneration, cyclic effects of endocrine glands, capillary permeability, immunological phenomena, and to calcification of cartilage, bone, and teeth.

Other work (Ruzick, 1927; Hurst, 1933; Gellhorn and Regnier, 1936; Pearce, 1936; Lowry *et al.*, 1942a, b, 1946; Horvath, 1946; Berg, 1947; Rhoades, 1948) indicates that the local environment of cells may change as a result of aging, tumor growth, regeneration and irradiation, and that these changes may in some cases be correlated with the rate at which cells may exchange substances with the blood. In this connection the work of L. Friedman and E. O. Kraemer (1930) on the diffusion of various substances in gelatine gels may be mentioned. These workers found that the magnitudes of the diffusion coefficients of several nonelectrolytes in a 10% gelatine gel were only about one-half of their values in pure water.

III. Blood-tissue fluid exchange. E. H. Starling (1895–96) formulated the hypothesis that the exchange of fluid between the blood and the interstitial spaces depends of the balance between the hydrostatic pressure excess of the blood, which tends to filter fluid into the tissues, and the colloid osmotic pressure excess of the blood, which tends to filter fluid from the tissue into the blood. The mechanism depends on the relative impermeability of the capillary wall to the blood colloids, and on the low hydrostatic pressure of the extracellular fluid. Both points are confirmed experimentally (Pappenheimer *et al.*, 1948, 1951; Field *et al.*, 1932; McMaster, 1946). The work of E. M. Landis (1927, 1934, 1946), J. F. Danielli (1940), and J. R. Pappenheimer *et al.* (*loc. cit.*) has confirmed the details of Starling's hypothesis.

While Starling's hypothesis, as discussed above, accounts for blood-tissue fluid exchange, and, together with a consideration of the lymphatic system, adequately accounts for the maintenance of blood volume, etc., the exchange of many substances between the blood and the extracellular spaces occurs so rapidly that only diffusion through the capillary wall seems to provide a mechanism which could give the required speed.

IV. Blood-tissue molecular exchange. That the process of filtration through the capillary wall of substances in solution in the blood plasma is not rapid enough to account for the observed rate of transfer across the wall follows directly from the estimates of the maximum filtration rates observed. Pappenheimer *et al.* (1951) calculate that the ratio of the rate of transfer by diffusion to the rate of transfer by filtration during very rapid filtration is about 116 for glucose, 83 for raffinose, and 27 for inulin, when the extracellular concentration is zero. The ratio becomes equal to unity only when the ratio of the concentration in the extracellular space to the concentration in the capillary is about 0.99 for glucose and raffinose and 0.96 for inulin. Furthermore, the work of C. Hyman *et al.* (1952) provides direct evidence that even when a tissue is becoming edematous the rate of capillary exchange is not measurably affected.

Much experimental work has been devoted to the features of blood-tissue exchange (Dominguez *et al.*, 1935–36; Manery *et al.*, 1939a, b, 1941a, b; Hevesy and Jacobsen, 1940; Hahn and Hevesy, 1941; Gellhorn *et al.*, 1944; Kruhøffer, 1946a, b; Flexner *et al.*, 1948; Morel and Marois, 1949; Jones, 1951; Pappenheimer *et al.*, *loc. cit.*; Renkin, 1952).

The experimental work mentioned above, with the exception of that of Pappenheimer *et al.* and of Renkin, was done with intact animals, and the exchange relations observed are greatly complicated by the fact that various organs receive in any time interval very different amounts of blood per unit volume of the organ. Thus H. B. Jones (*loc. cit.*) gives as the volume of blood per unit volume of tissue per minute received by the various organs of a man of approximately 70 kg. weight: thyroid, 3.0 to 10.0; kidney, 5.0; brain, 0.50; marrow, 0.15; liver, 1.10; muscle, skin, fat, and bone, about 0.026. The work of Gellhorn *et al.* (1944) mentioned above also indicates that an injected substance is removed from the blood by the organs with the larger perfusion rates and restored to the blood as the substance is gradually transferred to the organs with the lesser perfusion rates. It seems apparent from this data on the blood perfusion rates of various organs that the large differences in these rates may mask changes due to other differences between the tissues of various organs. In experiments in which the blood concentration of an injected substance is followed in an intact animal such seems to be the case. Work such as that of Pappenheimer *et al.* (*loc. cit.*), which partially avoids these complications by perfusing a relatively homogeneous tissue, may provide data reflecting more clearly the influence of the capillary permeability and the extracellular matrix upon the blood-tissue exchange relations.

The experimental data on blood-tissue exchange is usually described quite accurately by a sum of exponential terms, with two such terms being sufficient in many cases, although occasionally one is adequate (Flexner *et al.*, *loc. cit.*), and sometimes as many as five terms are needed (Jones, *loc. cit.*).

The time constants of the exponential terms have been interpreted in terms of total capillary wall area, and the over-all permeability coefficients of the capillary wall, neglecting the distribution process in the tissue, and frequently neglecting the differences in the blood perfusion rates of the various tissues. Thus T. Teorell (1937a, b) reviewed the work of several earlier investigators and provided a theoretical model for blood-tissue exchange which does not distinguish between tissues with respect to their perfusion rates.

However, the work of I. Bloch (1941, 1943) and of R. Smith and M. Morales (1944a, b) and of M. Morales and R. Smith (1944, 1945a, b, 1948) does take into account in a detailed fashion many important tissue parameters and provides a rational interpretation of the experimentally determined coefficients. The work of Smith and Morales particularly seems to provide a rationale for the investigation of the exchange of lipid soluble substances which takes into account the most pertinent physiological factors.

The work of N. A. Michels (1936), B. W. Zweifach (1936–37, 1939, 1940a, b, 1950) and R. Chambers and B. W. Zweifach (1940, 1944, 1946, 1948, 1949) on the functional anatomy of the capillaries has made clear that the capillary bed of most tissues is composed of two types of capillaries, whose functional significance must be taken into account in any complete theory of the blood-tissue exchange.

V. The capillary bed. The work of Chambers and Zweifach (*loc. cit.*) has disclosed that, functionally, the capillary bed consists of central channels with side branches. Starting at the smallest arteriole, the central channel is composed of a metarteriole, with a discontinuous array of typical muscle cells along it, imparting vasomotion to the vessels which are about eight to fifteen microns in diameter. Next comes the proximal portion of the arteriolo-venular or a-v capillary with atypical muscle cells which cause changes in the diameter of the a-v capillary only under abnormal conditions. The distal portion of the a-v channel is invested with a coat of connective tissue. These a-v capillaries fuse to form nonmuscular venules about fifteen to twenty-five microns in diameter; these venules have a relatively heavy coat of investing connective tissue. Branching off the proximal muscular portion of the central channels are precapillaries which have a proximal muscle-invested portion about twenty to thirty microns in diameter. The true capillaries anastomose freely and return to the distal portion of the a-v channels or to the nonmuscular venules. The angle at which the first of the precapillaries branches from a given a-v capillary is more than ninety degrees. Later branches leave at successively smaller angles, and the true capillaries return to the a-v channels at a very slight angle. The junction of the a-v and precapillaries is marked by endothelial folds which act as sphincters, apparently controlling the flow into the true capillaries. The true capillaries show only passive changes in diameter, which result from changes in the blood flow through them. Figure 1, based on the work of Zweifach, gives a schematic representation of the capillary anatomy.

The a-v channel normally has a continuous rapid blood flow through it, subject to recurrent vasomotion which consists of an irregular series of partial contractions of the metarteriole and the precapillary sphincters at intervals varying from thirty seconds to three minutes. Even when active flow through the true capillary is cut off, the capillary still has a fluid in it.

The angle of branching of the precapillaries from the central channel, and the relatively large diameter of the proximal portion of the precapillary, is apparently such as to maintain within the true capillary a more or less uniformly low hydrostatic pressure; perhaps less, for the greater portion of its length, than the colloid osmotic pressure of the blood.

Thus Zweifach and Chambers accept the general concept of Starling's hypothesis—that filtration from the capillaries occurs where the hydrostatic pressure exceeds the colloid osmotic pressure—but shift the locus of action so that filtration from the a-v capillary is believed to occur along most of its length, and absorption from the tissue spaces occurs along most of the length of the true capillary.

The ratio of the number of true capillaries to the number of a-v capillaries is a tissue characteristic and varies from less than 1 in the skin to more than 10 in the skeletal muscle (Zweifach, 1936–37).

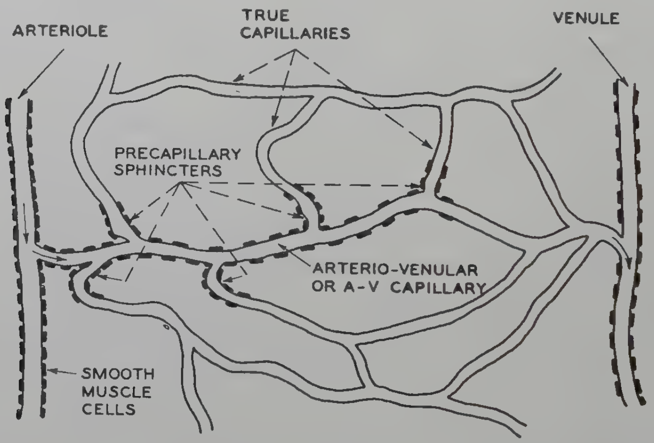

Figure 1. Schematic diagram of capillary bed

The unselective permeability of the capillary wall in most regions of the body is adequately explained by the "pore" theory (Chambers and Zweifach, 1947; Zweifach, 1940b; Pappenheimer *et al., loc. cit.*). According to this, the endothelial cells of the capillary secrete a cement substance, which binds together the endothelial cells and constitutes a matrix between them which is porous. The matrix permits the passage of low molecular weight substances with little hindrance. A decrease in the calcium ion content or the pH of the perfusing fluid softens the cement and enhances its dissipation, and thus results in an increase in the rate of filtration and diffusion from the capillary. In addition to the layer of endothelial cells, the capillary wall has an endocapillary layer, which is very thin and noncellular, lining the inner surface. This may be a layer of adsorbed protein

(Zweifach, 1940b). A closely adhering, investing layer of argentophil fibrils, the pericapillary sheath, covers the outer surface of the capillary.

P. Rous *et al.* (1930, 1931), F. Smith *et al.* (1931, 1932), and Zweifach (1940) have observed what they interpret as an increase in the capillary permeability from the arterial to the venous end. Danielli and Stock (1944) have disputed the interpretation but not the observation. However, the reasoning of Danielli and Stock does not consider the functional anatomy of the capillary bed as outlined above, and hence must be questioned.

VI. A tissue model for blood-tissue exchange. On the basis of the foregoing discussion, an idealized model of a tissue will be constructed and the exchange between the blood and the tissue in such a model will be considered. The considerations are restricted to the exchange of substances which are lipid-insoluble. Substances which enter the red cells in appreciable amounts, which are appreciably adsorbed on blood proteins, or which undergo chemical changes at appreciable rates in either the blood or the extracellular spaces—all such substances require special considerations which would considerably complicate the equations to be developed and hence are excluded from the present treatment. Lipid-soluble substances may pass through the endothelial cells of the capillaries and also through the walls of the smaller arterioles and venules. Hence such substances are also excluded. The model applies only to a homogeneous tissue whose blood supply and ratio of extracellular to cellular phases are everywhere constant. The length of all capillaries, both a-v and true, will be taken as equal everywhere. The radii of the capillaries, and the number and location of the active capillaries will be assumed constant during the process considered.

Since the capillaries form an irregular network with the arterial end of one capillary likely to be adjacent to the venous end of another, only variations of concentrations in the extracellular spaces in a direction normal to the capillary axis are considered.

Furthermore, the filtration rate along the capillary will be taken as constant, positive along the length of the a-v capillary and negative along the length of the true capillary. This is perhaps partially justified by the observations of the gradient in capillary permeability mentioned above. Thus if the capillary becomes more permeable toward the venous end, the rate of filtration through the wall would be greater at the venous end, if the pressure were equal to that at the arterial end. But the pressure is lower, and hence, as an approximation, the filtration rate along the length of the capillary will be taken to be constant.

The number of parameters which must be taken into account is so large and the number of combinations of these occurring in the equations to be developed is so great that the Glossary of Symbols appended at the end of this work (see p. 258) may assist the reader in interpreting the equations.

Distances along both the a-v and true capillaries will be designated by z. The length L is defined as the average functional length of the a-v capillaries, i.e., the length along which exchange between the blood and tissue may occur at an appreciable rate. At the arterial end $z = 0$ and at the venous end $z = L$. The true capillaries form an irregular anastomosing network in which the length of any one capillary is not readily defined directly. But the ratio of the total length of all active true capillaries in a homogeneous tissue, i.e., those through which blood is flowing, to the total length of all a-v capillaries in the tissue could be determined. This ratio, which will be designated by A, and called the activity ratio, is assumed to be known. Then in our model we replace the actual distribution of capillaries by arrays consisting of one a-v capillary, of length L, and A true capillaries also all of length L, all in parallel. In the model, $z = 0$ where blood enters the true capillaries, and $z = L$ where blood flows out of them.

We asssume that the mean velocity of the blood entering the a-v capillaries in the homogeneous tissue is $v_1(0)$ and that entering the true capillaries is $v_2(0)$. Since we consider only substances in solution in the blood plasma, it is convenient to express the blood concentrations in terms of concentrations in the red cell-free, protein-free fraction $f_1(z)$ of the total blood volume which is in the a-v capillaries at any point z along the length of the capillary. Let $f_2(z)$ be the corresponding fractions of the blood in the true capillary. Since the blood entering the two types of capillaries may have different numbers of red cells per unit volume, even $f_1(0)$ and $f_2(0)$ may not be equal. Let r_1 and r_2 be the radii of the a-v and true capillaries, respectively.

We will assume that the bulk of the material filtered into or out of the capillaries is water, so that the changes in the volume of an element of blood or perfusate are due solely to water filtration. The product of the filtration constant by the net differences between the hydrostatic and osmotic pressures acting across the wall of the a-v capillary will be denoted by P_1. The corresponding quantity for the true capillary will be denoted by P_2. It is assumed that $P_1 > 0$ and $P_2 < 0$ for $0 \leq z \leq L$, where L is the length of the capillary. This assumption is in accordance with the concept of Zweifach and Chambers, discussed earlier, that filtration from the a-v capillary occurs along most of its length, and that absorption of fluid from the tissue spaces occurs along most of the length of the true capillaries.

Then the material balance equation for any element of length dz and volume $\pi r_1^2 dz$ along the a-v capillary is:

$$\pi r_1^2 d f_1(z)\, dz = [\pi r_1^2 f_1(z)\, v_1(z) - \pi r_1^2 f_1(z+dz)\, v_1(z+dz) \\ - 2\pi r_1 P_1 dz]\, dt\,. \tag{1}$$

The term on the left-hand side of the equation gives the accumulation of the fluid in the volume $\pi r_1^2 dz$, and the terms on the right are, in order, the amount of fluid entering the element, the amount leaving the venous end, and the amount filtering through the capillary wall.

Simplifying (1) and using Taylor's theorem, we have

$$\frac{\partial f_1}{\partial t} = -\frac{\partial f_1 v_1}{\partial z} - \frac{2P_1}{r_1}\,. \tag{2}$$

We will consider only the case where filtration is constant with respect to time. Then the solution of (2) is

$$f_1(z)\, v_1(z) = f_1(0)\, v_1(0) - \frac{2P_1}{r_1} z\,. \tag{3}$$

Thus, according to the assumptions made, an element of fluid moves more slowly as it approaches the venous end of the a-v capillary. Similarly, we find for the true capillary,

$$f_2(z)\, v_2(z) = f_2(0)\, v_2(0) - \frac{2P_2}{r_2} z\,. \tag{4}$$

We now consider the variation along the length of the a-v capillary of a substance in the fluid of the blood. Let $K_1(z,t)$ be its concentration in the cell-free, protein-free fluid. The amount entering an element of volume of an a-v capillary, $\pi r_1^2 dz$, in time dt is

$$\pi r_1^2 f_1(z)\, v_1(z)\, K_1(z, t)\, dt\,. \tag{5}$$

The amount leaving the venous end of the element is

$$\pi r_1^2 f_1(z+dz)\, v_1(z+dz)\, K_1(z+dz, t)\, dt\,. \tag{6}$$

The net amount leaving through the capillary wall is

$$2\pi r_1 [(k_1 + d_1 P_1)\, K_1(z, t) - k_1' E_1']\, dz dt\,, \tag{7}$$

where k_1 and k_1' are, respectively, the average permeability coefficients for exit and entrance of the substance through the capillary wall (these coefficients may be different in the blood vessels of the brain and other special tissues), d_1 is the distribution ratio giving the ratio of the concentration of the substance in the filtrate to the concentration in the protein-free plasma, and E_1' is the mean concentration of the substance in the extracellular fluid at the wall of the a-v capillary. The amount of the substance accumulating in the element of volume is

$$\pi r_1^2 dz\, dK_1(z, t) . \tag{8}$$

Since we have asumed that no inactivation or chemical changes occur in the blood, the material balance requires

$$\begin{aligned} \pi r_1^2 dz\, dK_1(z, t) = {} & [\pi r_1^2 f_1(z)\, v_1(z)\, K_1(z, t) \\ & - \pi r_1^2 f_1(z+dz)\, v_1(z+dz)\, K_1(z+dz, t)]\, dt \\ & - [2\pi r_1 (k_1 + d_1 P_1)\, K_1(z, t) - 2\pi r_1 k_1' E_1']\, dz\, dt . \end{aligned} \tag{9}$$

Simplifying this, we have

$$\begin{aligned} dz \frac{\partial K_1}{\partial t} = {} & f_1(z)\, v_1(z)\, K_1(z, t) - f_1(z+dz)\, v_1(z+dz) \\ & \times K_1(z+dz, t) - \frac{2}{r_1}(k_1 + d_1 P)\, K_1(z, t)\, dz + \frac{2}{r_1} k_1' E_1'(t)\, dz . \end{aligned} \tag{10}$$

Upon using Taylor's theorem and (3) we finally obtain

$$\frac{\partial K_1}{\partial t} = -f_1(z)\, v_1(z) \frac{\partial K_1}{\partial z} + \frac{2}{r_1}(P_1 - d_1 P_1 - k_1)\, K_1 + \frac{2}{r_1} k_1' E_1'(t) . \tag{11}$$

Essentially the same considerations apply to the true capillary, except that the filtration here is assumed to occur from the tissue into the capillary. Hence the net amount of the substance leaving through the wall of the true capillary in time dt is

$$2\pi r_2 [k_2 K_2(z, t) - (k_2' - d_2 P_2) E_2'(t)]\, dz\, dt . \tag{12}$$

Here k_2 and k_2' are the average permeability coefficients for exit and entrance of the material through the true capillary wall, d_2 is the distribution ratio of the filtrate, and E_2' is the mean concentration outside of the wall of the true capillary. Thus, by the same reasoning that produced equation (11), we obtain an equation for $K_2(z,t)$. This is

$$\frac{\partial K_2}{\partial t} = -f_2(z)\, v_2(z) \frac{\partial K_2}{\partial z} + \frac{2}{r_2}(P_2 - k_2)\, K_2 + \frac{2}{r_2}(k_2' - d_2 P_2) E_2'(t) . \tag{13}$$

We have neglected the radial concentration gradient in the capillary since it is likely to be very small.

We now consider the concentration of the substance in the extracellular and cellular phases. We use the previously defined activity ratio A and assume that each a-v capillary is surrounded by a cylinder of tissue of average radius AR. The average extracellular concentration in this cylinder will be called E_1 and the average intracellular concentration in the cells of this cylinder will be called C_1. Similarly we assume that each of the true capillaries in our model is surrounded by a cylinder of tissue of average radius R, with an average extracellular concentration E_2 and an average intracellular concentration C_2. If the number of a-v capillaries in an arbitrary volume V is N, and if we know A, L, and N, then the radii AR and R are given by the requirement that

$$V = [A^2R^2 + AR^2]\,\pi NL + B = \pi R^2 LNA\,(A+1) + B\,, \qquad (14)$$

where B is the volume occupied by the blood vessels larger than capillaries. The volume B is not likely to exceed about seven per cent of the total volume of any tissue. According to these definitions, $AR + R$ is an approximate measure of the average distance between a-v and true capillaries.

We will also assume that the amount of material removed from the tissue by the lymphatic system is negligible; hence the considerations are restricted to tissues in which the lymphatic drainage during the time considered is very small compared to the blood flow.

The gradient of concentration of the material in the extracellular phase at the surface of the a-v capillary is approximately (cf. Rashevsky, 1948, pp. 15–23)

$$\frac{2\,(E_1' - E_1)}{AR} \qquad (15)$$

where $AR/2$ is the approximate distance between the a-v capillary and the site where the true concentration may be supposed to be about equal to the average concentration. Then at the wall of the a-v capillary we have

$$[\,(k_1 + d_1P_1)\,K_{m1} - k_1'E_1'\,] = \frac{(E_1' - E_1)\,2\,Dgl}{AR}\,, \qquad (16)$$

where K_{m1} is the mean concentration in the protein-free plasma, D is the diffusion coefficient in the substance of the extracellular space, g is a factor given by the ratio of the cell-free area through which diffusion may occur to the total area (normal to the gradient of the concentration), and l is the ratio of the shortest distance between two points in the tissue to the distance which must be traveled between the two points without crossing any cell walls. The equation implies that the speed of diffusion in the extracellular space is very great relative to the speed of transport through the walls of the cells. Similarly, at the true capillary wall, we have

$$[k_2 K_{m2} - (k_2' - d_2 P_2) E_2'] = (E_2' - E_2)\frac{2Dgl}{R}. \tag{17}$$

The amount of the substance flowing into the cells in the region of the a-v capillary in time dt is approximately

$$\pi (A^2R^2 - r_1^2)\ [h_1 E_1 - h_2 C_1]\frac{bs}{v}\,dz\,dt, \tag{18}$$

where h_1 and h_2 are permeability coefficients for entrance to and exit from the cells, s/v is the cell surface to volume ratio, and b is the fraction of the extravascular space occupied by cells. The expression implies that the speed with which the substance distributes itself inside of the cells is very great relative to the rate at which it crosses the cell wall. The amount of the substance flowing from the region surrounding the a-v capillary into the regions surrounding the true capillaries is given approximately by

$$(E_1 - E_2)\, 2Dgl\,\frac{2\pi AR}{AR+R}\,dz\,dt. \tag{19}$$

Here

$$\frac{2(E_1 - E_2)}{AR+R}$$

is the approximate gradient at the boundary of the region and $2\pi ARdz$ is the approximate area normal to the gradient through which flow must occur.

The average net amount entering the region from the a-v capillary in time dt is

$$2\pi r_1[(k_1 + d_1 P_1)\,K_{m1}(t) - k_1' E_1']\,dz\,dt. \tag{20}$$

The amount accumulating in the extracellular phase around the a-v capillary is

$$\pi (A^2R^2 - r_1^2)\,a f_a\,dz\,dE_1, \tag{21}$$

where a is the fraction of the extravascular volume not occupied by cells, and f_a is the fraction of extracellular volume which is available for the distribution of the substance, i.e., not occupied by fibers or other material through which diffusion cannot occur.

Then the material balance requirement, together with (18), (19), (20), and (21), gives

$$\begin{aligned}\pi(A^2R^2 - r_1^2)\, a f_a\, dz\, dE_1 = &-(E_1 - E_2)\frac{4\pi D g l A R}{AR + R}\, dz\, dt \\ &+ 2\pi r_1 [\,(k_1 + d_1 P_1)\, K_{m1}(t) - k_1' E_1'\,]\, dz\, dt \\ &- \pi(A^2R^2 - r_1^2)\,[\,h_1 E_1 - h_2 C_1\,]\frac{b s}{v}\, dz\, dt .\end{aligned} \tag{22}$$

After cancellations and rearrangements, this becomes

$$\begin{aligned}\frac{dE_1}{dt} = &-\frac{4 D g l}{a f_a (A^2R^2 - r_1^2)}\left(\frac{A}{A+1}\right)(E_1 - E_2) + \frac{2 r_1 (k_1 + d_1 P_1)}{a f_a (A^2R^2 - r_1^2)}\, K_{m1} \\ &- \frac{2 r_1 k_1'}{a f_a (A^2R^2 - r_1^2)} E_1' - \frac{b s h_1}{a f_a v} E_1 + \frac{b s h_2}{a f_a v} C_1 .\end{aligned} \tag{23}$$

Similarly, the amount of material flowing into the cells in the region of the true capillary in time dt is approximately

$$\pi(R^2 - r_2^2)\,[\,h_1 E_2 - h_2 C_2\,]\frac{b s}{v}\, dz\, dt . \tag{24}$$

The amount of material flowing from the region of the true capillary to the region of the a-v capillary is approximately

$$(E_2 - E_1)\, 2 D g l \frac{2\pi R}{AR + R}\, dz\, dt . \tag{25}$$

Here

$$\frac{2\,(E_2 - E_1)}{AR + R}$$

is the approximate gradient at the boundary of the region and $2\pi R dz$ is the approximate area normal to the gradient through which flow must occur. The average net amount entering the region from the true capillary in time dt is

$$2\pi r_2 [\,k_2 K_{m2}(t) - (k_2' - d_2 P_2) E_2'\,]\, dz\, dt . \tag{26}$$

The amount accumulating in the extracellular phase around the true capillary is

$$\pi(R^2 - r_2^2)\, a f_a\, dz\, dE_2 . \tag{27}$$

Then, since no material is inactivated in the region, (24), (25), (26), and (27) give

$$\pi (R^2 - r_2^2)\, a f_a d\, z dE_2 = -\,(E_2 - E_1)\frac{4\pi D g l R}{AR + R} d\, z dt + 2\pi r_2\, [k_2 K_{m2}(t) \\ - (k_2' - d_2 P_2) E_2']\, d\, z dt - \pi (R^2 - r_2^2)\, [h_1 E_2 - h_2 C_2]\frac{b\,s}{v} d\, z dt . \tag{28}$$

After cancellations and rearrangements, this becomes

$$\frac{dE_2}{dt} = -\,(E_2 - E_1)\frac{4 D g l}{a f_a\, (R^2 - r_2^2)\, (A + 1)} + \frac{2\, r_2 k_2}{a f_a\, (R^2 - r_2^2)} K_{m2}(t) \\ - \frac{2\, r_2\, (k_2' - d_2 P_2)\, E_2'}{a f_a\, (R^2 - r_2^2)} - \frac{b\,s\,h_1}{a f_a v} E_2 + \frac{b\,s\,h_2}{a f_a v} C_2 . \tag{29}$$

Equations (23) and (29) imply that no net exchange of material occurs between one array of our model, consisting of an a-v capillary and its associated true capillaries, and another such array.

The concentration of the substance in the cells of the two regions must now be considered. The amounts of material flowing into the cells of the two regions are given by (18) and (24). The consumption of the material by the cells in the a-v region is assumed to be

$$q_1 + q_2\, (C_1 - C_0)\, , \tag{30}$$

where q_1 is the consumption in—say, moles per unit cell volume per unit time—and q_2 is a proportionality constant giving the change in the rate of consumption for a concentration different from some initial concentration C_0. Both q_1 and q_2 are negative for consumption. For production, q_2 will be assumed to be zero and q_1 positive. Then the amount of material produced or consumed in the a-v region is given by

$$\pi\, (A^2 R^2 - r_1^2)\, d\, z\, b f_b\, [\, q_1 + q_2\, (C_1 - C_0)\,]\, dt\, , \tag{31}$$

where f_b is the fraction of the cellular volume which is available for the distribution and production of the substance. The amount accumulating in the cells is given by

$$\pi\, (A^2 R^2 - r_1^2)\, d\, z\, b f_b dC_1\, . \tag{32}$$

Then (18), (31), and (32) give us

$$\pi\, (A^2 R^2 - r_1^2)\, d\, z\, b f_b dC_1 = \pi\, (A^2 R^2 - r_1^2)\, (h_1 E_1 - h_2 C_1)\frac{b\,s}{v}\, d\, z dt \\ + \pi\, (A^2 R^2 - r_1^2)\, d\, z\, b f_b\, [\, q_1 + q_2\, (C_1 - C_0)\,]\, dt\, . \tag{33}$$

Cancellation and rearrangement give us

$$\frac{dC_1}{dt}=\frac{s}{vf_b}[h_1E_1-h_2C_1]+q_1+q_2(C_1-C_0)\ . \tag{34}$$

Similar considerations for the cells of the true capillary region give us

$$\frac{dC_2}{dt}=\frac{s}{vf_b}[h_1E_2-h_2C_2]+q_1+q_2(C_2-C_0)\ . \tag{35}$$

We may now calculate the concentration of the substance in the venous blood leaving the capillary array. We will assume that edema is not developing. Hence the amount of fluid entering the array at any time must equal the amount leaving. Thus we have

$$\pi r_1^2 f_1(0)\,v_1(0)+A\pi r_2^2 f_2(0)\,v_2(0)=\pi r_1^2 f_1(L)\,v_1(L)+A\pi r_2^2 f_2(L)\,v_2(L)\ . \tag{36}$$

From (36), using (3) and (4), we obtain a relation which will be used later:

$$A=-\frac{r_1P_1}{r_2P_2}. \tag{37}$$

The amount of the substance leaving the a-v capillary in time *dt* is given by

$$\pi r_1^2 f_1(L)\,v_1(L)\,K_1(L,t)\,dt\ , \tag{38}$$

and the amount leaving the true capillaries of the array is

$$A\pi r_2^2 f_2(L)\,v_2(L)\,K_2(L,t)\,dt\ . \tag{39}$$

Then, after mixing the flows, the concentration of the protein-free venous plasma K_v is given by

$$K_v(t)=\frac{r_1^2 f_1(L)\,v_1(L)\,K_1(L,t)+A\,r_2^2 f_2(L)\,v_2(L)\,K_2(L,t)}{r_1^2 f_1(0)\,v_1(0)+A\,r_2^2 f_2(0)\,v_2(0)}. \tag{40}$$

VII. The transformation of the equations. The problem of the blood-tissue exchange has now been formulated in equations (11), (13), (16), (17), (23), (29), (34), and (35). These equations, together with (3), (4), and (40), are sufficient to determine the concentration of a substance in the venous blood, at the walls of the a-v and true capillaries, and in the cells of the two regions, as well as the average extracellular concentration in the two regions—all in terms of the concentration in the arterial blood, the blood velocity in the two types of capillaries, and the various tissue parameters.

The solutions of the equations are most conveniently obtained by means of the Laplace transformation (Churchill, 1944). That is, we associate with each function $F(t)$ its Laplace transform $f(p)$, defined by

$$f(p) = \int_0^\infty e^{-pt} F(t)\, dt\,.$$

We will let x_i', x_i, y_i, w_i, and w_{mi} be the Laplace transforms of E_i', E_i, C_i, K_i, and K_{mi}, respectively, with $i = 1, 2$.

The transform of (11) is

$$pw_1 - K_0 = -f_1(z)\, v_1(z) \frac{dw_1(z, p)}{dz} + \frac{2}{r_1}(P_1 - d_1P_1 - k_1)\, w_1(z, p) + \frac{2k_1'}{r_1} x_1'(p)\,, \tag{41}$$

where K_0 is the initial concentration in the capillary, assumed to be constant. Then

$$f_1(z)\, v_1(z) \frac{dw_1}{dz} = -\left[p - \frac{2}{r_1}(P_1 - d_1P_1 - k_1)\right] w_1 + \frac{2k_1'}{r_1} x_1'(p) + K_0\,. \tag{42}$$

Let us put

$$\beta_1 = p - \frac{2}{r_1}(P_1 - d_1P_1 - k_1) \qquad \text{and} \qquad \mu_1 = \frac{2k_1'}{r_1}\,.$$

Then, using (3), (42) becomes

$$\frac{dw_1}{-\beta_1 w_1 + \mu_1 x_1' + K_0} = \frac{dz}{f_1(z)\, v_1(z)} = \frac{dz}{f_1(0)\, v_1(0) - \frac{2P_1}{r_1} z}\,. \tag{43}$$

The solution of (43) is

$$\frac{w_1(z, p)\, \beta_1 - \mu_1 x_1' - K_0}{w_0(p)\, \beta_1 - \mu_1 x_1' - K_0} = \left(1 - \frac{2P_1 z}{r_1 f_{10} v_{10}}\right)^{\beta_1 (r_1/2P_1)}, \tag{44}$$

where $w_0(p)$ is the transform of the concentration in the protein-free plasma of the arterial blood, and $f_{10}v_{10} = f_1(0)v_1(0)$. The mean value of $w_1(z,p)$ along the a-v capillary is given by

$$\frac{w_{m1}(p)\, \beta_1 - \mu_1 x_1' - K_0}{w_0(p)\, \beta_1 - \mu_1 x_1' - K_0} = \frac{1}{L} \int_0^L \left(1 - \frac{2P_1 z}{r_1 f_{10} v_{10}}\right)^{r_1 \beta_1 / 2P_1} dz\,. \tag{45}$$

Calculating the integral, we finally have, putting

$$\gamma_1 = \frac{r_1}{2P_1}\left[p - \frac{2}{r_1}(P_1 - d_1P_1 - k_1)\right] \qquad \text{and} \qquad \lambda_1 = \frac{2P_1L}{r_1 f_{10}\, v_{10}},$$

$$\frac{w_{m1}\beta_1 - \mu_1 x_1' - K_0}{w_0\beta_1 - \mu_1 x_1' - K_0} = \frac{1}{\lambda_1(1+\gamma_1)}\left[1 - (1-\lambda_1)^{1+\gamma_1}\right],$$

or

$$w_{m1} = \left(w_0 - \frac{K_0}{\beta_1}\right)\left(\frac{1-(1-\lambda_1)^{1+\gamma_1}}{\lambda_1(1+\gamma_1)}\right) + \frac{\mu_1}{\beta_1}x_1'\left(1 - \frac{1-(1-\lambda_1)^{1+\gamma_1}}{\lambda_1(1+\gamma_1)}\right) + \frac{K_0}{\beta_1}. \tag{46}$$

We will also need

$$w_1(L, p) = \left(w_0 - \frac{K_0}{\beta_1}\right)(1-\lambda_1)^{\gamma_1} + \frac{\mu_1}{\beta_1}x_1'(1 - [1-\lambda_1]^{\gamma_1}) + \frac{K_0}{\beta_1}. \tag{47}$$

The transform of (13) is

$$pw_2(z, p) - K_0 = -f_2(z)\, v_2(z)\frac{dw_2(z, p)}{dz} + \frac{2}{r_2}(P_2 - k_2)\, w_2(z, p) + \frac{2}{r_2}(k_2' - d_2P_2)\, x_2'(p). \tag{48}$$

Then

$$f_2(z)\, v_2(z)\frac{dw_2}{dz} = -\left[p - \frac{2}{r_2}(P_2 - k_2)\right]w_2 + \frac{2}{r_2}(k_2' - d_2P_2)\, x_2'(p) + K_0. \tag{49}$$

Putting

$$\beta_2 = p - \frac{2}{r_2}(P_2 - k_2), \qquad \mu_2 = \frac{2}{r_2}(k_2' - d_2P_2),$$

and using (4), we have

$$\frac{dw_2}{-\beta_2 w_2 + \mu_2 x_2' + K_0} = \frac{dz}{f_{20}\, v_{20} - \frac{2P_2}{r_2}z}, \tag{50}$$

where $f_{20}v_{20} = f_2(0)v_2(0)$. The solution of (50) is

$$\frac{w_2(z, p)\,\beta_2 - \mu_2 x_2' - K_0}{w_0(p)\,\beta_2 - \mu_2 x_2' - K_0} = \left(1 - \frac{2P_2 z}{r_2 f_{20}\, v_{20}}\right)^{\beta_2(r_2/2P_2)}. \tag{51}$$

Equation (51) implies that the concentration of the substance in the protein-free plasma entering any true capillary is the same as that entering an a-v capillary. This is undoubtedly not correct, but may be approximately so, since many true capillaries originate fairly close to the arterial end of the a-v capillaries. The mean value of w_2 along the true capillary is

$$\frac{w_{m2}(p)\,\beta_2 - \mu_2 x_2' - K_0}{w_0(p)\,\beta_2 - \mu_2 x_2' - K_0} = \frac{1}{L}\int_0^L \left(1 - \frac{2P_2 z}{r_2 f_{20} v_{20}}\right)^{\beta_2 (r_2/2P_2)} dz\,. \tag{52}$$

The right-hand side is equal to

$$\frac{1}{\lambda_2(1+\gamma_2)}\,[1 - (1-\lambda_2)^{1+\gamma_2}]\,, \tag{53}$$

where

$$\gamma_2 = \frac{r_2}{2P_2}\left[p - \frac{2}{r_2}(P_2 - k_2)\right] \quad \text{and} \quad \lambda_2 = \frac{2P_2 L}{r_2 f_{20} v_{20}}\,.$$

Then

$$\begin{aligned} w_{m2}(p) = {} & \left(w_0 - \frac{K_0}{\beta_2}\right)\left(\frac{1-(1-\lambda_2)^{1+\gamma_2}}{\lambda_2(1+\gamma_2)}\right) \\ & + \frac{\mu_2}{\beta_2}\, x_2'\left(1 - \frac{1-(1-\lambda_2)^{1+\gamma_2}}{\lambda_2(1-\gamma_2)}\right) + \frac{K_0}{\beta_2}\,. \end{aligned} \tag{54}$$

We will also need

$$w_2(L, p) = \left(w_0 - \frac{K_0}{\beta_2}\right)(1-\lambda_2)^{\gamma_2} + \frac{\mu_2}{\beta_2}\, x_2'[1 - (1-\lambda_2)^{\gamma_2}] + \frac{K_0}{\beta_2}\,. \tag{55}$$

The transforms of (16) and (17) are

$$[(k_1 + d_1 P_1)\, w_{m1} - k_1' x_1'] = (x_1' - x_1)\frac{2Dgl}{AR} \tag{56}$$

and

$$[k_2 w_{m2} - (k_2' - d_2 P_2)\, x_2'] = (x_2' - x_2)\frac{2Dgl}{R}\,. \tag{57}$$

Using the notations

$$\nu_1 = \frac{k_1' + \dfrac{2Dgl}{AR}}{k_1 + d_1 P_1}\,, \qquad \nu_2 = \frac{k_2' - d_2 P_2 + \dfrac{2Dgl}{R}}{k_2}\,;$$

$$\rho_1 = \frac{2Dgl}{AR(k_1 + d_1 P_1)}\,, \qquad \rho_2 = \frac{2Dgl}{Rk_2}\,;$$

we have for (56) and (57)

$$w_{m1} - \nu_1 x_1' + \rho_1 x_1 = 0\,, \tag{58}$$

$$w_{m2} - \nu_2 x_2' + \rho_2 x_2 = 0\,. \tag{59}$$

The transforms of (23), (29), (34), and (35), after the introduction of the E_0's and C_0's as the initial values of the extracellular and cellular concentrations, are:

$$\begin{aligned} px_1 - E_0 = & -\frac{4Dgl}{af_a(A^2R^2 - r_1^2)}\left(\frac{A}{A+1}\right)(x_1 - x_2) + \frac{2r(k_1 + d_1P_1)}{af_a(A^2R^2 - R_1^2)} \\ & \times w_{m1} - \frac{2r_1k_1'}{af_a(A^2R^2 - r_1^2)}x_1' - \frac{bsh_1}{af_av}x_1 + \frac{bsh_2}{af_av}y_1\,; \end{aligned} \tag{60}$$

$$\begin{aligned} px_2 - E_0 = & -\frac{4Dgl}{af_a(R^2 - r_2^2)\ (A+1)}(x_2 - x_1) + \frac{2r_2k_2}{af_a(R^2 - r_2^2)}w_{m2} \\ & - \frac{2r_2(k_2' - d_2P_2)}{af_a(R^2 - r_2^2)}x_2' - \frac{bsh_1}{af_av}x_2 + \frac{bsh_2}{af_av}y_2\,; \end{aligned} \tag{61}$$

$$py_1 - C_0 = \frac{sh_1}{vf_b}x_1 - \frac{sh_2}{vf_b}y_1 + \frac{q_1 - q_2C_0}{p} + q_2y_1\,; \tag{62}$$

$$py_2 - C_0 = \frac{sh_1}{vf_b}x_2 - \frac{sh_2}{vf_b}y_2 + \frac{q_1 - q_2C_0}{p} + q_2y_2\,. \tag{63}$$

The following notation will be used for the combinations of constants in (60) to (63):

$$\xi_1 = \frac{4glD}{af_a(A^2R^2 - r_1^2)}\left(\frac{A}{A+1}\right); \qquad \xi_2 = \frac{4glD}{af_a(R^2 - r_2^2)}\left(\frac{1}{A+1}\right);$$

$$\phi_1 = \frac{2r_1(k_1 + d_1P_1)}{af_a(A^2R^2 - r_1^2)}; \qquad \phi_2 = \frac{2r_2k_2}{af_a(R^2 - r_2^2)};$$

$$\psi_1 = \frac{2r_1k_1'}{af_a(A^2R^2 - r_1^2)}; \qquad \psi_2 = \frac{2r_2(k_2' - d_2P_2)}{af_a(R^2 - r_2^2)};$$

$$\sigma_1 = \frac{bsh_1}{af_av}; \qquad \sigma_2 = \frac{sh_2}{vf_b}; \qquad \omega = q_1 - q_2C_0\,.$$

Using these abbreviations in (60) to (63), we have

$$px_1 - E_0 = -\xi_1x_1 + \xi_1x_2 + \phi_1w_{m1} - \psi_1x_1' - \sigma_1x_1 + \sigma_2\frac{bf_b}{af_a}y_1, \tag{64}$$

$$px_2 - E_0 = -\xi_2x_2 + \xi_2x_1 + \phi_2w_{m2} - \psi_2x_2' - \sigma_1x_2 + \sigma_2\frac{bf_b}{af_a}y_2, \tag{65}$$

$$py_1 - C_0 = \sigma_1\frac{af_a}{bf_b}x_1 - \sigma_2y_1 + \frac{\omega}{p} + q_2y_1, \tag{66}$$

$$py_2 - C_0 = \sigma_1\frac{af_a}{bf_b}x_2 - \sigma_2y_2 + \frac{\omega}{p} + q_2y_2\,. \tag{67}$$

From (66) and (67), we have

$$y_i = \frac{\sigma_1 \dfrac{a f_a}{b f_b} x_i + C_0 + \dfrac{\omega}{p}}{p + \sigma_2 - q_2}, \qquad i = 1, 2 . \tag{68}$$

Introducing (68) into (64) and (65), we get, after some rearrangements,

$$x_1 \left(p + \xi_1 + \sigma_1 - \frac{\sigma_1 \sigma_2}{p + \sigma_2 - q_2} \right) - \xi_1 x_2 - \phi_1 w_{m1} + \psi_1 x_1' - E_0 \left\{ 1 + \frac{C_0}{E_0} \frac{b f_b}{a f_a} \frac{\sigma_2 \left(p + \dfrac{\omega}{C_0} \right)}{p\,(p + \sigma_2 - q_2)} \right\} = 0 , \tag{69}$$

$$x_2 \left(p + \xi_2 + \sigma_1 - \frac{\sigma_1 \sigma_2}{p + \sigma_2 - q_2} \right) - \xi_2 x_1 - \phi_2 w_{m2} + \psi_2 x_2' - E_0 \left\{ 1 + \frac{C_0}{E_0} \frac{b f_b}{a f_a} \frac{\sigma_2 \left(p + \dfrac{\omega}{C_0} \right)}{p\,(p + \sigma_2 - q_2)} \right\} = 0 . \tag{70}$$

If we let

$$\alpha_1 = p + \xi_1 + \sigma_1 - \frac{\sigma_1 \sigma_2}{p + \sigma_2 - q_2},$$

$$\alpha_2 = p + \xi_2 + \sigma_1 - \frac{\sigma_1 \sigma_2}{p + \sigma_2 - q_2},$$

$$\beta_0 = E_0 \left\{ 1 + \frac{C_0}{E_0} \frac{b f_b}{a f_a} \frac{\sigma_2 \left(p + \dfrac{\omega}{C_0} \right)}{p\,(p + \sigma_2 - q_2)} \right\};$$

then (69) and (70) become

$$\alpha_1 x_1 - \xi_1 x_2 - \phi_1 w_{m1} + \psi_1 x_1' = \beta_0 , \tag{71}$$

$$\alpha_2 x_2 - \xi_2 x_1 - \phi_2 w_{m2} + \psi_2 x_2' = \beta_0 . \tag{72}$$

Let us now introduce the symbols

$$\zeta_1 = \frac{1 - (1 - \lambda_1)^{1+\gamma_1}}{\lambda_1 (1 + \gamma_1)}, \qquad \zeta_2 = \frac{1 - (1 - \lambda_2)^{1+\gamma_2}}{\lambda_2 (1 + \gamma_2)},$$

$$Z_1 = \left[w_0 - \frac{K_0}{\beta_1} \right] \zeta_1 \beta_1 + K_0 , \qquad Z_2 = \left[w_0 - \frac{K_0}{\beta_2} \right] \zeta_2 \beta_2 + K_0 .$$

Using this notation in (46) and (54), and collecting the equations (58), (59), (71), and (72) for convenience of reference, we have:

$$x_1'(1-\zeta_1)\mu_1 - w_{m1}\beta_1 = -Z_1\,, \tag{73}$$

$$x_2'(1-\zeta_2)\mu_2 - w_{m2}\beta_2 = -Z_2\,, \tag{74}$$

$$\nu_1 x_1' - \rho_1 x_1 - w_{m1} = 0\,, \tag{75}$$

$$\nu_2 x_2' - \rho_2 x_2 - w_{m2} = 0\,, \tag{76}$$

$$\psi_1 x_1' + \alpha_1 x_1 - \xi_1 x_2 - \phi_1 w_{m1} = \beta_0\,, \tag{77}$$

$$\psi_2 x_2' - \xi_2 x_1 + \alpha_2 x_2 - \phi_2 w_{m2} = \beta_0\,. \tag{78}$$

These equations, (73) to (78), together with (40), (47), (55), and (68), are necessary and sufficient to determine the venous concentration, E_1, E_2, C_1, C_2, E_1', and E_2' in terms of the arterial concentration, the flow rates in the two types of capillaries, and the various tissue parameters.

Using (75) and (76) in (73), (74), (77), and (78) to eliminate w_{m1} and w_{m2} we obtain

$$x_1'[\mu_1(1-\zeta_1) - \beta_1\nu_1] + \beta_1\rho_1 x_1 = -Z_1\,, \tag{79}$$

$$x_2'[\mu_2(1-\zeta_2) - \beta_2\nu_2] + \beta_2\rho_2 x_2 = -Z_2\,, \tag{80}$$

$$x_1'(\psi_1 - \phi_1\nu_1) + x_1(\alpha_1 + \phi_1\rho_1) - \xi_1 x_2 = \beta_0\,, \tag{81}$$

$$x_2'(\psi_2 - \phi_2\nu_2) - \xi_2 x_1 + x_2(\alpha_2 + \phi_2\rho_2) = \beta_0\,. \tag{82}$$

VIII. The steady state. We may use equations (79) to (82) to get an estimate of the relative importance of the various parameters in their influence upon the steady state concentrations of a substance when the arterial concentration has been constant long enough for the steady state to be assumed.

We use the theorem that if a limit exists for a function $F(t)$ as t approaches infinity, then $pf(p)$ approaches the same limit as p approaches zero through positive values, where $f(p)$ is the Laplace transform of $F(t)$ and p is the transformation parameter (Doetsch, 1950, p. 458). Hence assuming the existence of a steady state, which seems plausible on physical grounds, we have for (79) to (82), where the various functions of p, i.e., $a_1, a_2, \beta_0, \beta_1, \beta_2, \gamma_1, \gamma_2, \zeta_1$, and ζ_2 must be evaluated at the limit as $p \to +0$,

$$E_1' [\mu_1 (1 - \zeta_1) - \beta_1 \nu_1] + E_1 \beta_1 \rho_1 = \lim_{p \to +0} - pZ_1 , \tag{83}$$

$$E_2' [\mu_2 (1 - \zeta_2) - \beta_2 \nu_2] + E_2 \beta_2 \rho_2 = \lim_{p \to +0} - pZ_2 , \tag{84}$$

$$E_1' (\psi_1 - \phi_1 \nu_1) + E_1 (a_1 + \phi_1 \rho_1) - E_2 \xi_1 = \lim_{p \to +0} p\beta_0 , \tag{85}$$

$$E_2' (\psi_2 - \phi_2 \nu_2) - E_1 \xi_2 + E_2 (a_2 + \phi_2 \rho_2) = \lim_{p \to +0} p\beta_0 . \tag{86}$$

As an illustration, we will consider the production of a substance in the cells at a constant rate q_1 moles per cubic centimeter per second. Hence we take q_2 equal to zero. We will also take $k_1 = k_2 = k_1' = k_2'$, and $r_1 = r_2$; P_1, d_1P_1, P_2, and d_2P_2 will be neglected relative to k_1, since even during extremely rapid filtration into the tissue from the capillaries, k_1 is likely to be from twenty-five to two hundred times as large as P_1 or P_2. The exact ratio depends on the molecular weight of the substance, the ratio being higher for the lower molecular weights (Pappenheimer *et al.*, 1951). Since λ_1 and λ_2 are the ratios of the leakage through the capillary wall to the fluid flow into the capillary, we may put as a good approximation, when edema is not developing,

$$1 - \lambda_1 = e^{-\lambda_1} \qquad \text{and} \qquad 1 - \lambda_2 = e^{-\lambda_2} .$$

For while λ_1 and λ_2 may range from 0.001 to 0.2 (Danielli and Stock, *loc. cit.*), the higher values occur only during the rapid development of edema, and we restrict ourselves to the case of no net filtration into or out of the blood.

With these assumptions, we have the following values for the various coefficients in equations (83) to (86):

$$a_1 = \xi_1 ; \qquad a_2 = \xi_2 ; \qquad \lim_{p \to +0} p\beta_0 = \frac{b f_b}{a f_a} q_1 ; \qquad \beta_1 = \beta_2 = \frac{2 k_1}{r_1} ;$$

$$\gamma_1 = -1 + d_1 + \frac{k_1}{P_1} ; \qquad \gamma_2 = -1 + \frac{k_1}{P_2} ; \qquad \zeta_1 = \frac{r_1 f_{10} v_{10}}{2L k_1} (1 - e^{-2Lk_1/r_1 f_{10} v_{10}}) ;$$

$$\zeta_2 = \frac{r_1 f_{20} v_{20}}{2L k_1} (1 - e^{-(2Lk_1/r_1 f_{20} v_{20})}) ;$$

$$\lim_{p \to +0} - pZ_1 = - K(0, \infty) \frac{f_{10} v_{10}}{L} (1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}) ;$$

$$\lim_{p \to +0} - pZ_2 = - K(0, \infty) \frac{f_{20} v_{20}}{L} (1 - e^{-(2Lk_2/r_1 f_{20} v_{20})}) .$$

Let us also assume that $A = 1$; this may be approximately the case in mammalian skeletal muscle under the experimental conditions used by Pappenheimer *et al.* (*loc. cit.*), especially with the smaller perfusion rates. If we assume that $f_{10}v_{10} = f_{20}v_{20}$, then the coefficients of equations (83) and (84) become identical, as do those of (85) and (86), and $E_1' = E_2'$ and $E_1 = E_2$. This assumption is unlikely to be good, since according to the observations of Zweifach, $f_{20}v_{20} < f_{10}v_{10}$, but the lack of exact data on the relative flow rates, the fact that the assumption seems unlikely to affect the illustration qualitatively, and the simplicity gained seem to justify its use. Using these assumptions, equations (83) and (86) reduce, after some rearrangements, to

$$-E_1'\left\{\frac{r_1 f_{10} v_{10}}{2Lk_1}\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right) + \frac{2Dgl}{Rk_1}\right\} + E_1 \frac{2Dgl}{Rk_1} = -K(0, \infty)\frac{r_1 f_{10} v_{10}}{2Lk_1}\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right), \tag{87}$$

$$E_1' - E_1 = -q_1 b f_b \frac{R(R^2 - r_1^2)}{4r_1 Dgl}. \tag{88}$$

Solving these for E_1' and E_1, we get

$$E_1' = K(0, \infty) + q_1 b f_b \frac{L}{f_{10} v_{10}}\left[\left(\frac{R}{r_1}\right)^2 - 1\right]\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right)^{-1}, \tag{89}$$

$$E_1 = K(0, \infty) + q_1 b f_b \times \left[\left(\frac{R}{r_1}\right)^2 - 1\right]\left\{\frac{Rr_1}{4Dgl} + \frac{L}{f_{10} v_{10}}\left(1 - e^{-(2Lk_1/r_1 f_{10} v_{10})}\right)^{-1}\right\}. \tag{90}$$

We now need numerical estimates of the various parameters. Mammalian striated muscle will be considered since this tissue is marked by large changes in activity. The average length of a capillary is about 0.7 mm. and the average radius is about 5×10^{-4} cm. (Rous *et al.*, 1930; Krogh, 1929). Jones (*loc. cit.*) gives the average perfusion rate of muscle as 0.01 to 0.030 volumes of blood per volume of tissue per minute. Pappenheimer *et al.* (1951) give an estimate of 70 cm.^{2} per gm. of muscle as the capillary wall area. This estimate is much smaller than those given by Krogh (*loc. cit.*). Using equation (14) with B, the volume of blood vessels larger than capillaries taken as 7% of the total volume, we obtain $R = 36.4 \times 10^{-4}$ cm. and $2N = 3.18 \times 10^5$ capillaries of both types per gm. Furthermore, we obtain $v_{10} = 1.33 \times 10^{-3}$ cm. per sec. for the blood velocity corresponding to a perfusion rate of 0.02 per minute. Taking f_{10} as 0.5, we have $f_{10}v_{10} = 0.67 \times 10^{-3}$ cm. per sec. Hence $L/f_{10}v_{10} \approx 100$.

However, the estimate of 70 cm.^{2} per gm. used in these calculations may be low. The value 140 cm.^{2} per gm. gives $L/f_{10}v_{10} \approx 50$. This value will be used in all calculations and graphs. Naturally, v_{10} depends on the activity, but since more capillaries open up during activity, and since the values of both E_1 and E_1' are more dependent upon the values assumed for R than those assumed for $L/f_{10}v_{10}$, we will keep this fixed and consider only variations in R, Dgl, and k_1.

The values of Dgl depend on the molecular weight of the substance considered, on the state of the extracellular matrix, and on the geometry of the distribution of the cells in the tissue. The factor gl is likely to be about 0.1, since g is about 0.15 and l is about 0.66. The values of k_1 are dependent on the molecular weight of the substance considered, and upon the state of the capillary wall, which may be altered as a result of various physiological changes. The data of Pappenheimer *et al.* (1951) permit an estimate of k_1 to be made for various molecules. Thus for glucose, $k_1 \approx 10^{-4}$ cm. per sec., for sucrose, $k_1 \approx 0.6 \times 10^{-4}$, for raffinose $k_1 \approx 0.4 \times 10^{-4}$, for inulin $k_1 \approx 0.05 \times 10^{-4}$, and for NaCl, $k \approx 1.6 \times 10^{-4}$. We will consider variations in Dgl from 10^{-8} to 10^{-5} cm.^{2} per sec. and in k_1 from 10^{-5} to 10^{-3} cm. per sec.

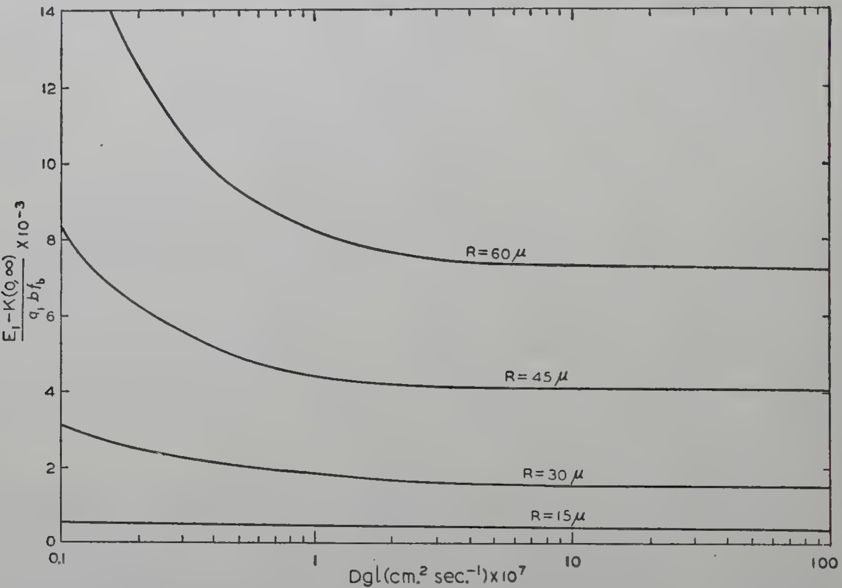

FIGURE 2. Graph of Equation (90). Values of parameters are: $L/f_{10}v_{10} = 50$ sec.; $r_1 = 5 \times 10^{-4}$ cm.; $k_1 = 10^{-4}$ cm. per sec.

Figure 2 shows the dependence of the ratio of $E_1 - K(0, \infty)$ to q_1bf_b

upon *Dgl* for four values of R. This ratio is much more dependent upon R than *Dgl*. Thus for a produced substance of about the molecular weight of glucose, the ratio is 400 for $R = 15\mu$, 1760 for $R = 30\mu$, 4000 for $R = 45\mu$, and 7300 for $R = 60\mu$.

Figure 3 shows the ratio of $E_1 - K(0, \infty)$ to $E_1' - K(0, \infty)$ as a function of *Dgl* for various values of R. Rather large differences between the average concentration and the concentration at the capillary wall may exist for the smaller values of *Dgl* if $K(0, \infty)$ is small. Thus if $K(0, \infty)$ is zero, the ratio of E_1 to E_1' for $Dgl = 10^{-7}$ cm.² per sec. is 1.038 for $R = 15\mu$, 1.075 for $R = 30\mu$, 1.112 for $R = 45\mu$, and 1.150 for $R = 60\mu$.

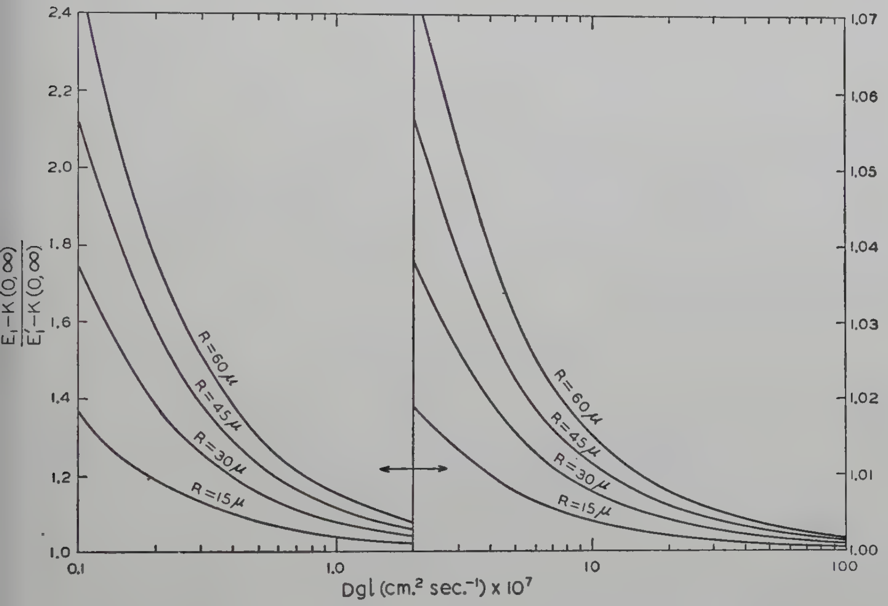

FIGURE 3. Graph of the ratio of equation (90) to equation (91). Values of parameters are: $L/f_{10}v_{10} = 50$ sec.; $r = 5 \times 10^{-4}$ cm.; $k_1 = 10^{-4}$ cm. per sec.

Turning now to a consideration of the average intracellular concentration C_1, we have from either equation (34) or (68) that in the steady state with constant production q_1,

$$C_1 = q_1 \frac{v f_b}{s h_2} + \frac{h_1}{h_2} E_1. \tag{91}$$

The variation in C_1 with constant q_1 is dependent on the average external concentration through the ratio of h_1 to h_2. If we assume that h_1 and h_2 are of the same order of magnitude, and that the cell radius is about 10^{-3} cm., then with $f_b \approx 0.5$ and $h_2 \approx 10^{-5}$ cm. per sec. we have, roughly, that the concentration in the cell at any time is about seventeen times that concentration produced in one second in unit volume by a source of strength q_1, plus the external concentration. The external concentration, as we have seen, is possibly several hundred to several thousand times the concentration which would be produced in a unit volume in one second by a source of strength q_1.

Hence it appears likely that the intracellular concentration of a substance produced in the cell may be influenced to a marked extent by the external concentration and thus by the diffusion coefficient of the extracellular material and the permeability coefficient of the capillary wall.

IX. Transient conditions. In order to investigate the influence of the diffusion coefficient of the extracellular material, and the permeability coefficient of the capillary wall upon the speed with which a substance introduced into the blood distributes itself, we will again resort to some drastic approximations. We will assume that $A = 1$, $k_1 = k_2 = k_1' = k_2'$, $r_1 = r_2$, $f_{10}v_{10} = f_{20}v_{20}$, and that $|\lambda_1| << 1$ and $|\lambda_2| << 1$. Using the last assumptions, we find that

$$\lim_{|\lambda_1| \to 0} \zeta_1 = \lim_{|\lambda_1| \to 0} \frac{1 - (1 - \lambda_1)^{1+\gamma_1}}{\lambda_1 (1 + \gamma_1)} = 1 \tag{92}$$

and

$$\lim_{|\lambda_2| \to 0} \zeta_2 = \lim_{|\lambda_2| \to 0} \frac{1 - (1 - \lambda_2)^{1+\gamma_2}}{\lambda_1 (1 + \gamma_1)} = 1 . \tag{93}$$

The set of equations (79) to (82) now reduces to

$$-x_1'\beta_1\nu_1 + x_1\beta_1\rho_1 = -Z_1 , \tag{94}$$

$$x_1'(\psi_1 - \phi_1\nu_1) + x_1(\alpha_1 - \xi_1 + \phi_1\rho_1) = \beta_0 . \tag{95}$$

Let us consider the case in which the substance does not penetrate the cells, or penetrates them so slowly, relative to the speed of its distribution in the extracellular space, that we may assume that none of the material has entered the cells during the time required for a quasi-steady state to be attained in the extracellular space. Thus we assume that a substance is suddenly introduced into the blood in such a way that its arterial concentration remains constant. Then, if none of the substance was present initially, we have

$$Z_1 = \frac{K\beta_1}{p}; \qquad \beta_0 = 0 \tag{96}$$

where K is the constant arterial concentration.

Solving equations (94) and (95) for x_1 and x_1', using these assumptions, we have

$$x_1' = \frac{K[\alpha_1 - \xi_1 + \phi_1\rho_1]}{p[\nu_1(\alpha_1 - \xi_1 + \phi_1\rho_1) + \rho_1(\psi_1 - \phi_1\nu_1)]}, \tag{97}$$

$$x_1 = -\frac{K[\psi_1 - \phi_1\nu_1]}{p[\nu_1(\alpha_1 - \xi_1 + \phi_1\rho_1) + \rho_1(\psi_1 - \phi_1\nu_1)]}. \tag{98}$$

By our assumptions we have $\sigma_1 \approx \sigma_2 \approx 0$, and we also assume, as before, that $|P_1| < < k_1$ and $|P_2| < < k_2$. Then the denominators of both equations (97) and (98) reduce to

$$p[\nu_1 p + \nu_1\phi_1\rho_1 - \phi_1\rho_1^2]. \tag{99}$$

We also have

$$\alpha_1 - \xi_1 + \phi_1\rho_1 = p + \phi_1\rho_1 \tag{100}$$

and

$$\psi_1 - \phi_1\nu_1 = -\phi_1\rho_1. \tag{101}$$

Using (99), (100), and (101) in (97) and (98), we get

$$x_1' = \frac{K(p + \phi_1\rho_1)}{p[\nu_1 p + \nu_1\phi_1\rho_1 - \phi_1\rho_1^2]} \tag{102}$$

and

$$x_1 = \frac{K\phi_1\rho_1}{p[\nu_1 p + \nu_1\phi_1\rho_1 - \phi_1\rho_1^2]}. \tag{103}$$

Inverting these equations in p by routine methods of the Laplace transformation technique, we have, after some rearrangements,

$$E_1' = K\left\{1 - \frac{\rho_1}{1 + \rho_1} e^{-t(\phi_1\rho_1)/(1+\rho_1)}\right\}; \tag{104}$$

$$E_1 = K\{1 - e^{-t(\phi_1\rho_1)/(1+\rho_1)}\}. \tag{105}$$

A check on the first of these equations is provided by a comparison of $E_1'(0)$ computed from equation (16) with $E_1'(0)$ computed from (104). Both computations give

$$E_1' = \frac{K}{\nu_1}. \tag{106}$$

We have from (105)

$$\frac{dE_1}{dt} = K\frac{\phi_1\rho_1}{1 + \rho_1} e^{-t(\phi_1\rho_1)/(1+\rho_1)}, \tag{107}$$

and

$$\frac{dE_1(0)}{dt} = K\frac{\phi_1\rho_1}{1 + \rho_1}. \tag{108}$$

Figures 4 and 5 show

$$\frac{1 + \rho_1}{\phi_1\rho_1}$$

as a function of *Dgl* and k_1, respectively, for four values of R. These graphs give the time at which E_1 attains approximately 63% of the capillary concentration K, as well as the ratio of K to $dE_1(0)/dt$.

It may be noted that for a molecule of the weight of glucose, the time constant is 2.1 sec. for $R = 15\mu$, 10 sec. for $R = 30\mu$, 24 sec. for $R = 45\mu$, and 46 sec. for $R = 60\mu$. The time constant for the distribution process, for any fixed R, is markedly dependent on *Dgl* in the range 10^{-8} to 2×10^{-7} cm.^{2} per sec. and on k_1 in the whole range considered. Thus for molecules as large, or larger than, glucose the distribution time is very much dependent on the characteristics of the extracellular matrix. The permeability of the capillary wall greatly influences the distribution time for substances of any molecular weight.

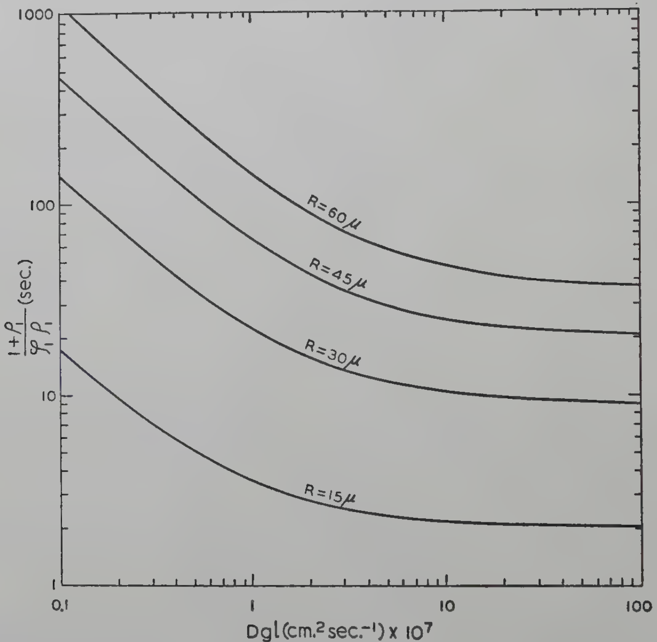

FIGURE 4. Graph of the reciprocal of the time constant of equation (105). Values of parameters are: $af_a = 0.1$; $r_1 = 5 \times 10^{-4}$ cm.; $k_1 = 10^{-4}$ cm. per sec.

However, the approximation that λ_1 and λ_2 are negligible compared to unity renders the treatment of doubtful value for more than the very start of the process of distribution, for these approximations, of course, imply that the concentration of the substance is everywhere the same along the length of the capillary and that the amount removed from the blood is negligible compared to the amount flowing through the capillary in any given interval of time.

X. Discussion and conclusion. The treatment of capillary exchange developed above, while undoubtedly approximate and of limited validity, does indicate that both the diffusion coefficient of the extracellular matrix and the permeability coefficient of the capillary wall are important parameters in the distribution of substances in tissue. Changes in the diffusion coefficient of the extracellular material are not so important as changes in the capillary permeability. Both parameters are subject to change, and changes in these parameters are followed by relatively large changes in both the steady state cellular and extracellular concentrations and changes in the initial rate at which a suddenly introduced substance distributes itself. Since the metabolism of cells is undoubtedly influenced greatly by the concentrations within them of various substances, it appears that significant changes in cell metabolism may occur as a result of alterations in either of these parameters.

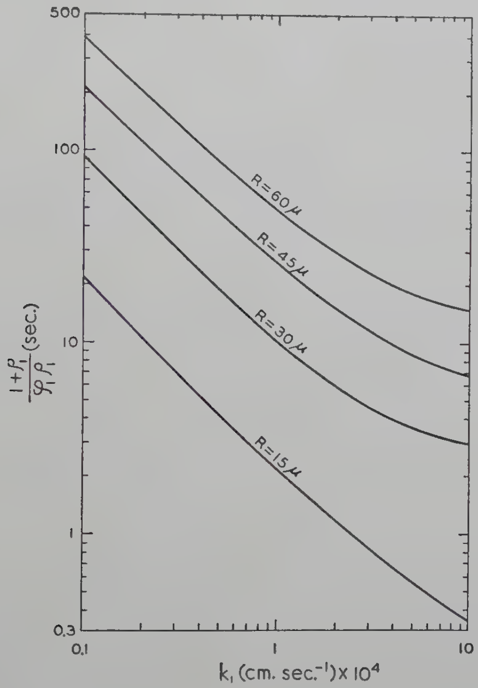

FIGURE 5. Graph of the reciprocal of the time constant of equation (105). Values of the parameters are: $af_a = 0.1$; $r_1 = 5 \times 10^{-4}$ cm.; $Dgl = 10^{-6}$ cm.^{2} per sec.

The consequence of a change in the ratio of the number of true capillaries to the number of a-v capillaries has been investigated only in so far as this may be correlated with changes in R. It is hoped that a more comprehensive investigation of this problem will form the subject of a later paper.

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GLOSSARY OF SYMBOLS

A = the activity ratio, the ratio of the total length of all active true capillaries to the total length of all a-v capillaries in a homogeneous tissue, also the ratio of the number of active true capillaries to the number of a-v capillaries in the tissue model

AR = radius of cylinder of tissue associated with each a-v capillary

a = the ratio of the extracellular volume to the total extravascular volume

b = the ratio of the cellular volume to the total extravascular volume

C_0 = the initial intracellular concentration

C_1 = the average intracellular concentration in the region of the a-v capillaries at any time $t > 0$

C_2 = the average intracellular concentration in the region of the true capillaries at any time $t > 0$

D = the diffusion coefficient in the substance of the extracellular space

d_1 = distribution ratio, the ratio of the concentration in the filtrate from the a-v capillaries to the concentration in the protein-free plasma

d_2 = similar to d_1, but for the true capillaries

E_0 = initial extracellular concentration, assumed to be the same everywhere

E_1 = average extracellular concentration in the region of the a-v capillaries at any time $t > 0$

E_2 = average extracellular concentration in the region of the true capillaries at any time $t > 0$

E_1' = extracellular concentration at the wall of the a-v capillary at time $t > 0$

E_2' = extracellular concentration at the wall of the true capillary at time $t > 0$

f_1 = ratio of the volume of the cell-free, protein-free fluid of the blood to the total blood volume in the a-v capillary

$f_{10} = f_1(0)$

f_2 = similar to f_1 but for the true capillary

$f_{20} = f_2(0)$

f_a = ratio of the extracellular volume available for diffusion to the total extracellular volume

f_b = ratio of the cellular volume available for distribution of the substance to the total cell volume

g = ratio of the area normal to the concentration gradient in the extracellular space, through which diffusion may occur, to the total area

h_1 = permeability coefficient of the cell wall for entrance of the substance into the cell

h_2 = permeability coefficient of the cell wall for exit of the substance from the cell

K_0 = initial concentration of the substance in both the a-v and true capillaries, assumed to be constant

K_1 = concentration of the substance in the a-v capillary, $0 \leq x \leq L$, for the time $t > 0$

K_2 = concentration of the substance in the true capillary, $0 \leq z \leq L$, for time $t > 0$

K_{m1} = mean concentration in the a-v capillary for any time $t > 0$

K_{m2} = mean concentration in the true capillary for any time $t > 0$

K_v = venous concentration of the cell-free, protein-free fluid of the blood at any time $t > 0$

k_1 = permeability coefficient of the a-v capillary for exit of substance

k_1' = permeability coefficient of the a-v capillary for entrance of the substance

k_2 = similar to k_1, but for the true capillary

k_2' = similar to k_1', but for the true capillary

L = average length of the a-v and true capillaries, assumed to be equal

l = the ratio of the shortest distance between two points in the tissue to the average distance between the two points which must be traveled while not going through any cell

N = total number of a-v capillaries in an arbitrary volume of a homogeneous tissue

P_1 = product of the filtration coefficient by the net pressure acting across the a-v capillary wall, assumed to be constant along the length of the capillary and greater than zero

P_2 = product of the filtration coefficient by the net pressure acting across the true capillary wall, assumed to be constant along the length of the capillary and less than zero

p = Laplace transformation parameter with respect to t

q_1 = rate of production per unit volume, or rate of consumption per unit volume when concentration in cell is C_0

q_2 = rate of change of consumption with respect to the cellular concentration

R = radius of cylinder of tissue associated with each true capillary

r_1 = radius of the a-v capillary

r_2 = radius of the true capillary

s = average surface area of any cell of a homogeneous tissue

t = time

v = average cell volume

v_1 = velocity of the blood in the a-v capillary

v_2 = velocity of the blood in the true capillary

$v_{10} = v_1(0)$
$v_{20} = v_2(0)$
w_1 = Laplace transform of K_1
w_2 = Laplace transform of K_2
w_{m1} = Laplace transform of K_{m1}
w_{m2} = Laplace transform of K_{m2}
$w_0 = w_1(0,p) = w_2(0,p)$
x_1 = Laplace transform of E_1
x_1' = Laplace transform of E_1'
x_2 = Laplace transform of E_2
x_2' = Laplace transform of E_2'
y_1 = Laplace transform of C_1
y_2 = Laplace transform of C_2
z = distance along either a-v or true capillary, measured from arterial end

$$a_1 = p + \xi_1 + \sigma_1 - \frac{\sigma_1\sigma_2}{p + \sigma_2 - q_2}, \qquad a_2 = p + \xi_2 + \sigma_1 - \frac{\sigma_1\sigma_2}{p + \sigma_2 - q_2}$$

$$\beta_0 = E_0\left\{ 1 + \frac{C_0}{E_0}\,\frac{b\,f_b}{a\,f_a}\,\frac{\sigma_2\left(p + \frac{\omega}{C_0}\right)}{p\,(p + \sigma_2 - q_2)} \right\}$$

$$\beta_1 = p - \frac{2}{r_1}(P_1 - d_1P_1 - K_1) = \frac{2P_1}{r_1}\,\gamma_1, \qquad \beta_2 = p - \frac{2}{r_2}(P_2 - k_2) = \frac{2P_2}{r_2}\,\gamma_2$$

$$\gamma_1 = \frac{r_1}{2P_1}\left[p - \frac{2}{r_1}(P_1 - d_1P_1 - k_1) \right], \qquad \gamma_2 = \frac{r_2}{2P_2}\left[p - \frac{2}{r_2}(P_2 - k_2) \right]$$

$$Z_1 = \left(w_0 - \frac{K_1}{\beta_1}\right)\zeta_1\beta_1 + K_0, \qquad Z_2 = \left(w_0 - \frac{K_0}{\beta_2}\right)\zeta_2\beta_2 + K_0$$

$$\zeta_1 = \frac{1 - (1 - \lambda_1)^{1+\gamma_1}}{\lambda_1(1 + \gamma_1)}, \qquad \zeta_2 = \frac{1 - (1 - \lambda_2)^{1+\gamma_2}}{\lambda_2(1 + \gamma_2)}$$

$$\lambda_1 = \frac{2P_1L}{r_1 f_{10}\, v_{10}}, \qquad \lambda_2 = \frac{2P_2L}{r_2 f_{20}\, v_{20}}$$

$$\mu_1 = \frac{2\,k_1'}{r_1}, \qquad \mu_2 = \frac{2\,(k_2' - d_2P_2)}{r_2}$$

$$\nu_1 = \frac{k_1' + \frac{2\,D\,gl}{AR}}{k_1 + d_1P_1}, \qquad \nu_2 = \frac{k_2' - d_2P_2 + \frac{2\,D\,gl}{R}}{k_2}$$

$$\xi_1 = \frac{4\,D\,gl}{a\,f_a\,(A^2R^2 - r_1^2)}\left(\frac{A}{A+1}\right), \qquad \xi_2 = \frac{4\,D\,gl}{a\,f_a\,(R^2 - r_2^2)}\left(\frac{1}{A+1}\right)$$

$$\rho_1 = \frac{2\,D g l}{A R\,(k_1 + d_1 P_1)}\,, \qquad \rho_2 = \frac{2\,D g l}{R k_2}$$

$$\sigma_1 = \frac{b\,s\,h_1}{a\,f_a\,v}\,, \qquad \sigma_2 = \frac{s\,h_2}{v\,f_b}$$

$$\phi_1 = \frac{2\,r_1\,(k_1 + d_1 P_1)}{a\,f_a\,(A^2 R^2 - r_1^2)}\,, \qquad \phi_2 = \frac{2\,r_2 k_2}{a\,f_a\,(R^2 - r_2^2)}$$

$$\psi_1 = \frac{2\,r_1 k_1'}{a\,f_a\,(A^2 R^2 - r_1^2)}\,, \qquad \psi_2 = \frac{2\,r_2\,(k_2' - d_2 P_2)}{a\,f_a\,(R^2 - r_2^2)}$$

$$\omega = q_1 - q_2 C_0$$

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BULLETIN OF
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THE DISTRIBUTION OF MEMBRANE CURRENT IN NERVE WITH LONGITUDINAL LINEARLY INCREASING APPLIED CURRENT

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The distribution of membrane current in three models of nerve, when a longitudinal, linearly increasing current is applied, is derived. For the simple core conductor model it is shown that, if the region over which such a current is applied is large compared to the space constant of the model, the membrane current in the mid-portion of the region is a constant, independent of the distance, the time following the application of the current, and the impedance of the membrane. The effect of nonlinear membrane electrical properties is discussed. It is further shown that these conclusions apply equally to the case in which the simple model is surrounded by another concentric sheath (the double cable model). In this case the impedance of the sheath does not influence the membrane current in the mid-polar region. Finally, it is shown that the form of the solution for the saltatory model, for this type of applied current, is identical with that for the simple model.

Most methods of causing electrical currents to flow radially across the membrane of nerve for purposes of studying the effects of such "polarization" result in large spatial gradients of membrane current density in the vicinity of the electrodes. This difficulty has been overcome in some cases by the use of internal electrodes in nerve fibers which are large enough to accommodate them (Hodgkin and Huxley, 1939; Curtis and Cole, 1940; Marmont, 1949). A method of producing a truly wide polarizing electrode applicable to small nerve fibers was sought. This paper presents the mathematical analyses associated with the successful outcome of that search.

The necessary form of externally applied current such that the membrane current in the simple core conductor model is essentially constant over a large region has been known for a long time, viz., that the total longitudinal applied current should increase linearly with distance along the model. An approximation to such a distribution of applied current was achieved by workers in M. Cremer's laboratory as early as 1922 (Cremer, 1929, p. 274) in an effort to determine an absolute constant of excitation.

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This type of applied current has been used by the author to investigate the effect of polarization on the conduction velocity of frog nerve. A preliminary report of this work has appeared (Taylor, 1950b) and the details of the experimental procedures and results will be reported elsewhere. The author has also had considerable success in using this method of applying current to produce local, nonpropagated electrically induced contractures in large regions of frog sartorius muscle (Taylor, 1951).

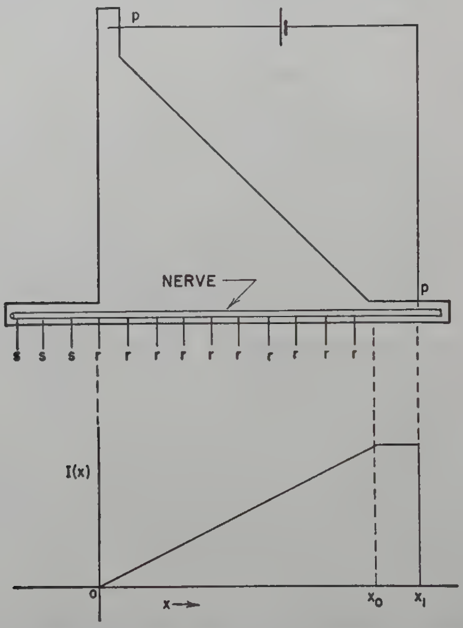

FIGURE 1. Schematic diagram of filter paper electrode used experimentally. *p-p:* polarizing electrodes, *s-s:* stimulating electrodes, *r-r:* recording electrodes. Lower graph shows ideal current density in vicinity of nerve, which is closely approached by this electrode shape. [Compare equation (19)].

Briefly, the electrode is a triangular shaped piece of filter paper (for nerve) thoroughly wet with Ringer's solution and mounted in a moist chamber. Voltage is applied at the two acute corners as indicated in Figure 1. The resulting current which flows along the lower edge of the filter paper, where the nerve is placed, increases in density in a linear manner from zero at the right-angled corner.

As will become clear in the analysis to follow, the current which will flow through the membrane of a fiber in a nerve so placed will be from outside inward if the direction of the current I and its first derivative dI/dx are the same, as in the illustration, and from inside outward otherwise. It will be assumed that the current density in the region of the nerve is proportional to the total longitudinal current flowing in some immediate vicinity of the fiber under consideration. It is shown in Part II that the presence of the resistive connective tissue sheath surrounding the nerve trunk does not invalidate this assumption.

The model for the nerve which will be first considered is the usual core conductor model with an applied longitudinal current which increases linearly from zero at $x = 0$. It would be quite possible to solve the problem for the exact type of applied current as indicated in Figure 1, but since the electrical properties are assumed to be linear, it is more convenient to utilize the principle of superposition, as will be seen later, so that it is only necessary to solve the problem for an applied current which increases from zero indefinitely. This will be done, following the derivation of a general integral solution which is applicable to any type of applied current.

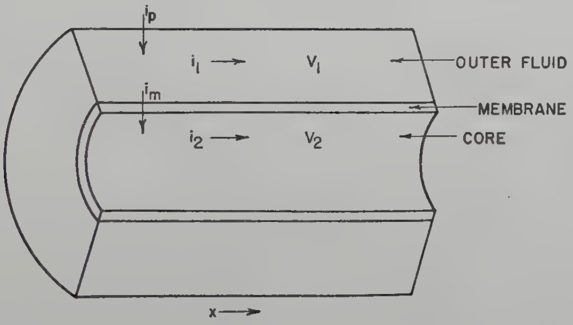

Figure 2. Geometry of continuous core conductor model considered. Section of infinitely long cylinder. For nomenclature see text.

Part I. Simple Core Conductor Model

A. Membrane current and voltage distribution in the simple core conductor model with linear, arbitrary membrane impedance in response to a constant, suddenly applied current of any form. Several treatments of the membrane voltage and current in the core conductor model, for various types of applied currents, both for the transient and for the steady states, are to be found in the literature (see Hodgkin and Rushton, 1946; Davis, in Lorente de Nó, 1947 for references). The assumptions which will be made here are those introduced by Weber in 1873 (Weinberg, 1941), with regard to the geometry of the model.

Assumptions (see Fig. 2).

1. The geometry of the system is an infinitely long cylinder with a conducting core, an external conducting layer, and a surface membrane with linear electrical characteristics.

2. The potential is constant throughout the core and the external fluid at any point along the length of the model.

3. The core and the external path are pure linear resistances.

4. Any initial membrane voltage will remain constant and can thus be neglected during the analysis.

Let:

x be the distance along the length of the cylinder in centimeters

t be the time in seconds

$p = s + jw$ be the complex variable associated with the unilateral Laplace transform; $s > s_0$, where s_0 is large enough to insure the convergence of the integrals involved; $j = \sqrt{-1}$

$m = 2\pi jf$ be the imaginary radian frequency associated with the bilateral Fourier transform

V_1 be the potential of the external fluid in volts

V_2 be the potential of the core in volts

$V_m = V_1 - V_2$ be the potential across the surface membrane in volts

$\overline{V}_m(x,p)$ be the Laplace transform of V_m with respect to time

$V(m,p)$ be the Fourier transform of $\overline{V}_m(x,p)$ with respect to distance, x

r_1 be the resistance per centimeter of the external fluid in ohm/cm

r_2 be the resistance per centimeter of the core in ohm/cm

r_m be the resistance of one centimeter length of membrane in ohm cm

i_1 be the longitudinal current flowing in the external fluid in amperes

i_2 be the longitudinal current flowing in the core in amperes

$I = i_1 + i_2$ be the total longitudinal current in the model in amperes

i_p be the "polarizing current" per centimeter length flowing radially into the external fluid from without the model. Clearly

$$i_p = \frac{\partial I}{\partial x}.$$

i_m be the current per centimeter length flowing inwardly across the membrane in amperes/cm

$Z(p)$ be the complex impedance of one centimeter length of membrane (see explicit definition later)

$$\lambda_c = \left(\frac{Z(p)}{r_1 + r_2}\right)^{1/2}$$

be the complex space constant

$$\lambda = \lim_{p \to \infty} \lambda_c = \left(\frac{r_m}{r_1 + r_2}\right)^{1/2}$$

be the real space constant

A simple application of Ohm's and Kirchoff's laws to this model yields the following relations immediately:

$$\frac{\partial V_1}{\partial x} = -r_1 i_1,$$

$$\frac{\partial V_2}{\partial x} = -r_2 i_2,$$

$$\frac{\partial i_2}{\partial x} = i_m.$$

Differentiating $V_m = V_1 - V_2$ with respect to x and substituting from the above, we have

$$\frac{\partial V_m}{\partial x} = -r_1 i_1 + r_2 i_2, \tag{1}$$

and, since $I = i_1 + i_2$, this can be written

$$\frac{\partial V_m}{\partial x} = i_2(r_1 + r_2) - I r_1. \tag{2}$$

Differentiating a second time and substituting

$$i_m = \frac{\partial i_2}{\partial x} \qquad \text{and} \qquad i_p = \frac{\partial I}{\partial x}$$

gives the well-known differential equation for the core conductor model, viz.,

$$\frac{\partial^2 V_m}{\partial x^2} - (r_1 + r_2) i_m = -r_1 i_p. \tag{3}$$

This development has been written out to show clearly the origin of the continuity conditions. The potentials V_1 and V_2 (and therefore V_m) must be continuous or an infinite current would flow through the nerve. The core current i_2 must be continuous or an infinite current would flow across the membrane. Since i_2 must be continuous, (2) states that the continuity of $\partial V_m/\partial x$ depends upon the continuity of $I(x)$. It is clear from physical considerations that if $I(x)$ is zero for large (positive or negative) x then V_m must approach zero for large (positive or negative) x.

In order to solve equation (3) for any type of applied current $I(x)$ (which, in general, may be a function of time), a relation between V_m and i_m in terms of the electrical characteristics of the membrane is needed. Equation (3) holds for any type of membrane (linear or nonlinear, function of time and distance, etc.). If it is assumed, as it is here, that the membrane electrical properties are linear, i.e., are characterized by parameters which are not functions of time or current flow, and are not functions of distance, the relation between V_m and i_m will *always* be a linear differential or integral equation with respect to time only, with constant coefficients. It may, however, be of infinite order (e.g., polarization impedance).

Under these conditions the complex impedance of the membrane will be defined in the following way: If we take the Laplace transform of the relation between V_m and i_m under discussion, we will obtain a linear algebraic equation in their transforms. On the assumption of all initial voltages and currents being zero, the ratio between the transform of V_m and that of i_m is called the complex impedance $Z(p)$. In terms of our nomenclature this can be written

$$Z(p) = \frac{\bar{V}_m}{\bar{i}_m}. \qquad (4)$$

If in this expression the real part of the complex variable p is set equal to zero ($p = s + jw$), the resulting expression $Z(jw)$ is identical with the complex impedance commonly encountered in electrical engineering. The presence of the nonzero real part here is associated with the fact that discontinuous driving functions are used (current applied suddenly) and amounts to the introduction of a convergence factor later on.

With the introduction of the membrane electrical characteristics in this form, and the assumption that the external current i_p is suddenly applied, we can proceed to derive an integral solution for equation (3) in terms of an arbitrary $Z(p)$ and $i_p(x)$. The solution will then be carried one step further for the case that $I = ax$ (where a is a constant) over a certain region, and some interesting properties of the solution for any membrane impedance will be pointed out. Finally, the complete solution for this type of applied current and a membrane with parallel resistance and capacity will be presented.

The first step is to take the Laplace transform of equation (3) with respect to time. The Laplace transform of V_m with respect to time is defined as

$$\bar{V}_m(x, p) = L_t\{ V_m(x, t) \} = \int_0^\infty V_m(x, t)\, e^{-pt} dt, \qquad (5)$$

and, similarly, the Laplace transform for i_m is $\bar{i}_m$.

By virtue of the known properties of the Laplace transform (see, e.g., Churchill, 1944), the transform of equation (3) for i_p suddenly applied (all initial currents and voltages zero) is

$$\frac{d^2 \bar{V}_m}{dx^2} - (r_1 + r_2)\, \bar{i}_m = \frac{-r_1 i_p}{p} \qquad (6)$$

and substitution of

$$Z(p) = \frac{\bar{V}_m}{\bar{i}_m}$$

gives

$$\frac{d^2 \bar{V}_m}{dx^2} - \frac{\bar{V}_m (r_1 + r_2)}{Z(p)} = \frac{-r_1 i_p}{p}. \tag{7}$$

Since the complex space constant is defined as

$$\lambda_c = \left(\frac{Z(p)}{r_1 + r_2}\right)^{1/2},$$

equation (7) becomes

$$\frac{\lambda_c^2 d^2 \bar{V}_m}{dx^2} - \bar{V}_m = \frac{-r_1 \lambda_c^2 i_p}{p}. \tag{8}$$

The Fourier transform of $\bar{V}_m(x,p)$ with respect to x is

$$V(m, p) = F_x\{\bar{V}_m(x, p)\} = \int_{-\infty}^{\infty} \bar{V}_m(x, p)\, e^{-mx} dx,$$

and, similarly, the Fourier transform of i_p is $\bar{i}_p$. Taking the Fourier transform of equation (8) gives us

$$\lambda_c^2 m^2 V - V = \frac{-r_1 \lambda_c^2 \bar{i}_p}{p}. \tag{9}$$

Solving this for V:

$$V = \frac{-r_1 \lambda_c^2 \bar{i}_p}{p(\lambda_c^2 m^2 - 1)}. \tag{10}$$

Equation (10) is the product of two transforms: $\bar{i}_p$, the inverse of which is i_p, and

$$\frac{-r_1 \lambda_c^2}{p(\lambda_c^2 m^2 - 1)}, \tag{11}$$

the inverse of which is (Campbell and Foster, 1942, pair #444)

$$\frac{r_1 \lambda_c e^{-|x/\lambda_c|}}{2p}. \tag{12}$$

The inverse of the product of two transforms can be expressed in terms of the inverses of the individual transforms by the application of the real convolution theorem (see, e.g., Churchill, 1944). This theorem states that if

$f(x)$, $g(x)$, and $h(x)$ have the respective transforms $F(m)$, $G(m)$, and $H(m)$, and if $F(m) = G(m)H(m)$, then

$$f(x) = \int_{-\infty}^{\infty} g(z)\, h(x - z)\, dz = \int_{-\infty}^{\infty} g(x - z)\, h(z)\, dz .$$

Applying this theorem to equation (10), the inverse $\overline{V}_m(x,p)$ becomes immediately

$$\overline{V}_m(x, p) = \frac{r_1 \lambda_c}{2p} \int_{-\infty}^{\infty} i_p(z) \exp\left(-\left|\frac{z - x}{\lambda_c}\right|\right) dz . \qquad (13)$$

Since by definition

$$\bar{\imath}_m = \frac{\overline{V}_m}{Z(p)} ,$$

we can write down

$$\bar{\imath}_m(x, p) = \frac{r_1}{2p\lambda_c(r_1 + r_2)} \int_{-\infty}^{\infty} i_p(z) \exp\left(-\left|\frac{z - x}{\lambda_c}\right|\right) dz . \qquad (14)$$

The complete solutions for the membrane current and voltage are then the inverse Laplace transforms of equations (13) and (14). Written out formally these are

$$V_m(x, t) = L^{-1}\{\overline{V}_m(x, p)\} = \frac{1}{2\pi} \int_{s_0 - j\infty}^{s_0 + j\infty} \overline{V}_m(x, p)\, e^{pt} dp , \quad t > 0 \qquad (15)$$

and

$$i_m(x, t) = L^{-1}\{\bar{\imath}_m(x, p)\} = \frac{1}{2\pi} \int_{s_0 - j\infty}^{s_0 + j\infty} \bar{\imath}_m(x, p)\, e^{pt} dp , \qquad t > 0 . \qquad (16)$$

Although equations (13), (14), (15), and (16) constitute the complete formal solution for the current through and the voltage across the membrane of the core conductor model as a function of time and space for any type of suddenly applied current and any (linear) membrane impedance, their explicit expansion may be simple, difficult, or impossible depending mostly upon the type of membrane impedance assumed. It shall be shown in the next section that from these expressions, certain general properties of the solutions may be elucidated without explicit expansion.

If one is interested only in the steady state solution, it is not necessary to evaluate the integrals in equations (15) and (16). A well-known theorem (see Churchill, 1944) states that if the function $f(t)$ has the Laplace transform $F(p)$, and if $pF(p)$ is analytic on the imaginary axis and the right half plane, then

$$\lim_{t \to \infty} f(t) = \lim_{p \to 0} pF(p) .$$

Applying this theorem to equations (13) and (14) gives the general steady state solutions as

$$V_m(x, \infty) = \frac{r_1 r_m}{2(r_1 + r_2)} \int_{-\infty}^{\infty} i_p(z)\, e^{-|z-x|/\Lambda} dz, \tag{17}$$

$$i_m(x, \infty) = \frac{r_1}{2(r_1 + r_2)} \int_{-\infty}^{\infty} i_p(z)\, e^{-|z-x|/\Lambda} dz. \tag{18}$$

The complex space constant λ_c disappears because its limit as $p \rightarrow 0$ is the real space constant λ.

These equations are readily integrated for any of the commonly encountered types of applied current.

B. Solution for applied current which increases linearly with distance; linear arbitrary membrane impedance. In the experimental work of the author (cf. Fig. 1), the applied current I had the following form:

$$I(x) = \begin{cases} 0, & x < 0, \\ ax, & 0 < x < x_0, \\ ax_0, & x_0 < x < x_1, \\ 0, & x_1 < x, \\ 0, & t < 0 \text{ for all } x. \end{cases} \tag{19}$$

While the solution for this type of current is readily obtained, a great deal of space can be saved by the application of the principle of superposition. This principle states that, if the electrical properties of any network are linear (characterized by parameters which are independent of time and current flow), and if the voltages V_a and V_b at any point in the network result from the application of currents I_a and I_b through some element, then, if $I_c = I_a + I_b$ is applied in the same element, the resulting voltage at the corresponding point is $V_c = V_a + V_b$.

Since the membrane voltage and current which results from the application of current of the form defined above for $x > x_0$ is well known (Hodgkin and Rushton, 1946; Davis, in Lorente de Nó, 1947), it can be seen that the only type of applied current which must be considered to get the total solution is of the form

$$I(x) = \begin{cases} 0, & x < 0, \\ ax, & x > 0, \\ 0, & t < 0. \end{cases} \tag{20}$$

The fact that $I(x)$ becomes infinite does not cause any embarrassment since it appears only as the derivative.

$$i_p = \frac{\partial I}{\partial x}\,.$$

Substituting the derivative of (20) into equations (13) and (14) and integrating gives the Laplace transform of the complete solution for this part of the problem, viz.,

$$\bar{V}_m(x,\,p) = \begin{cases} \dfrac{r_1\lambda_c^2 a}{2p}\,[\,e^{x/\lambda_c}]\,, & x \leqslant 0\,, \\[2ex] \dfrac{r_1\lambda_c^2 a}{2p}\,[2 - e^{-x/\lambda_c}]\,, & x \geqslant 0\,, \end{cases} \tag{21}$$

and

$$\bar{\imath}_m(x,\,p) = \begin{cases} \dfrac{r_1 a}{2p\,(r_1 + r_2)}\,[\,e^{x/\lambda_c}]\,, & x \leqslant 0\,, \\[2ex] \dfrac{r_1 a}{2p\,(r_1 + r_2)}\,[2 - e^{-x/\lambda_c}]\,, & x \geqslant 0\,. \end{cases} \tag{22}$$

These equations contain a result of great interest. Consider the region in which x is large enough to cause the quantity $|e^{-x/\lambda_c}|$ to be small. (It must not be forgotten that λ_c is complex.) If the real part of x/λ_c be denoted by $Re(x/\lambda_c)$, then

$$|\,e^{-x/\lambda_c}| = e^{-Re(x/\lambda_c)}\,,$$

so that, e.g., if $Re(x/\lambda_c)$ is greater than 3, $|e^{-x/\lambda_c}|$ will be less than 0.05.

For large values of $Re(x/\lambda_c)$, equation (22) becomes

$$\bar{\imath}_m(\infty,\,p) = \frac{r_1 a}{p\,(r_1 + r_2)}\,. \tag{23}$$

The inverse Laplace transform of (23) is a step function in time, viz.,

$$i_m(\infty,\,t) = \begin{cases} 0\,, & t < 0\,, \\[2ex] \dfrac{r_1 a}{(r_1 + r_2)}\,, & t > 0\,. \end{cases} \tag{24}$$

This tells us that, if we are far enough away from the point at which the applied current begins to increase linearly, and not too close to the point where it ceases to increase, the membrane current is not a function of the membrane impedance, the time following the application of current, or the distance along the model. It is also to be noticed that the membrane current is directly proportional to a, the gradient of the applied current.

The restriction that the value of x be large compared to the reciprocal of $Re(1/\lambda_c)$ means that these conclusions will obtain over a greater or lesser region depending upon the form of the membrane impedance, $Z(p)$ and the frequency range considered. It is clear that if the membrane impedance is of the same form as that of a network of resistors and capacitors (or of polarization capacities, see Cole, 1949) that the region will be larger for the transient state (high frequencies, p large) than for the steady state (p zero).

While the membrane current is essentially constant and independent of the properties of the membrane if the region over which the longitudinal linearly increasing current is long enough, the current flowing longitudinally in the core is a function of the membrane properties and is an increasing function of x. Since

$$i_m = \frac{\partial i_2}{\partial x},$$

the core current is given by

$$i_2 = \int_{-\infty}^{x} i_m dx .$$

The steady state core current is found by substituting equation (22) into this expression, multiplying by p, and letting p approach zero. The result is easily seen to be

$$i_2(x, \infty) = \begin{cases} \dfrac{r_1 a \lambda}{2(r_1 + r_2)} e^{x/\lambda}, & x \leqslant 0, \\[2ex] \dfrac{r_1 a \lambda}{2(r_1 + r_2)} [2x + \lambda e^{-x/\lambda}], & x \geqslant 0. \end{cases} \qquad (25)$$

In the experiments of the author the current was applied over a distance of five centimeters of frog sciatic-peroneal nerve (Taylor, 1950a, b). It was found that over the region from $x = 0.5$ to $x = 3.5$ cm., the velocity of conduction of the nervous impulse was independent of distance for any given amount of applied current up to block. With lambda about 0.3 cm. for this nerve, the core current must have increased over this region by a factor of about

$$\frac{i_2(3.5)}{i_2(0.5)} = 6.39,$$

so that it is hardly possible that the current in the core per se had any effect on the excitable properties of the membrane.

C. Complete solution for linearly increasing applied current; membrane with parallel resistance and capacity. If the membrane is considered to be a resistance and capacity in parallel, the relation between the voltage V_m and the current i_m at any point x is

$$i_m = \frac{V_m}{r_m} + \frac{C \partial V_m}{\partial t}, \tag{26}$$

where C is the capacity per unit length of membrane in farad/cm. Under the assumption that the initial voltage and current is zero, the Laplace transform of equation (26) is

$$\bar{i}_m(x, p) = \frac{\bar{V}_m}{r_m} + Cp\,\bar{V}_m,$$

and the membrane impedance is thus

$$Z(p) = \frac{\bar{V}_m}{\bar{i}_m} = \frac{r_m}{1 + t_m p}, \tag{27}$$

where t_m is the membrane time constant $r_m C$.

In this case, then, the complex space constant is related to the real space constant by

$$\lambda_c^2 = \frac{\lambda^2}{1 + t_m p}. \tag{28}$$

Substitution of equation (28) into the relations (21) and (22) gives the Laplace transforms, the inverses of which constitute the complete solutions for the membrane current and voltage for an applied current which is zero for x less than zero and increases linearly with x for x greater than zero (gradient $= a$). Making these substitutions, we have

$$\bar{V}_m(x, p) = \begin{cases} \dfrac{r_1 \lambda^2 a}{2p(1 + t_m p)}\left[e^{x\sqrt{1+t_m p}/\lambda}\right], & x \leqslant 0, \\[2ex] \dfrac{r_1 \lambda^2 a}{2p(1 + t_m p)}\left[2 - e^{-x\sqrt{1+t_m p}/\lambda}\right], & x \geqslant 0, \end{cases} \tag{29}$$

and

$$\bar{i}_m(x, p) = \begin{cases} \dfrac{r_1 a}{2p(r_1 + r_2)}\left[e^{x\sqrt{1+t_m p}/\lambda}\right], & x \leqslant 0, \\[2ex] \dfrac{r_1 a}{2p(r_1 + r_2)}\left[2 - e^{-x\sqrt{1+t_m p}/\lambda}\right], & x \geqslant 0. \end{cases} \tag{30}$$

The inverse Laplace transforms for the various terms in equations (29) and (30) can be found in the tables of G. A. Campbell and R. M. Foster (1942), pairs #825.5, #448, #819, and #415. All of the pairs of transforms listed by Campbell and Foster as Fourier integral pairs can be used as Laplace transforms where the restriction is found that $t > 0$ (their g). In pairs #825.5 and #819 it is necessary to allow their parameter gamma to approach zero. This is not permissible if these pairs are to be used as Fourier transform pairs, but can be shown to be legitimate if they are used as Laplace transform pairs, as in this case.

With the use of these pairs the inverses of equations (29) and (30) can be written down by inspection. Letting

$$X = \frac{x}{\lambda}, \qquad T = \frac{t}{t_m},$$

and introducing the error function:

$$\operatorname{erfc}(z) = 1 - \operatorname{erf}(z) = 1 - \frac{2}{\pi} \int_0^z e^{-w^2} dw$$

[tabulated values of error functions can be found in *Tables of Probability Functions* (1942)], the complete solutions are

$$V_m(x, t) = \begin{cases} \dfrac{r_1 \lambda^2 a}{4} \Big[e^{-X} \operatorname{erfc}\left(\sqrt{T} - \dfrac{X}{2\sqrt{T}}\right) \\ \qquad + e^{X} \operatorname{erfc}\left(-\sqrt{T} - \dfrac{X}{2\sqrt{T}}\right) \\ \qquad - 2 e^{-T} \operatorname{erfc}\left(\dfrac{-X}{2\sqrt{T}}\right) \Big], & x \leqslant 0, \\ \dfrac{r_1 \lambda^2 a}{4} \Big[4(1 - e^{-T}) - e^{X} \operatorname{erfc}\left(\sqrt{T} + \dfrac{X}{2\sqrt{T}}\right) \\ \qquad - e^{-X} \operatorname{erfc}\left(-\sqrt{T} + \dfrac{X}{2\sqrt{T}}\right) \\ \qquad + 2 e^{-T} \operatorname{erfc}\left(\dfrac{X}{2\sqrt{T}}\right) \Big], & x \geqslant 0, \end{cases} \tag{31}$$

and

$$i_m(x, t) = \begin{cases} \dfrac{r_1 a}{4(r_1 + r_2)} \Big[- e^{-X} \operatorname{erfc}\left(\sqrt{T} - \dfrac{X}{2\sqrt{T}}\right) \\ \qquad + e^{X} \operatorname{erfc}\left(-\sqrt{T} - \dfrac{X}{2\sqrt{T}}\right) \Big], & x \leqslant 0, \\ \dfrac{r_1 a}{4(r_1 + r_2)} \Big[4 + e^{X} \operatorname{erfc}\left(\sqrt{T} + \dfrac{X}{2\sqrt{T}}\right) \\ \qquad - e^{-X} \operatorname{erfc}\left(-\sqrt{T} + \dfrac{X}{2\sqrt{T}}\right) \Big], & x \geqslant 0. \end{cases} \tag{32}$$

Equations (31) and (32) are the complete solutions for the voltage across and the current through the membrane with parallel resistance and capacity, for the simple core conductor model, when the applied longitudinal current has the form given by (20). It is a simple matter of addition to get the complete form of the solution—if the applied current is of the form given by (19) as in Figure 1—by the use of equations (31) and

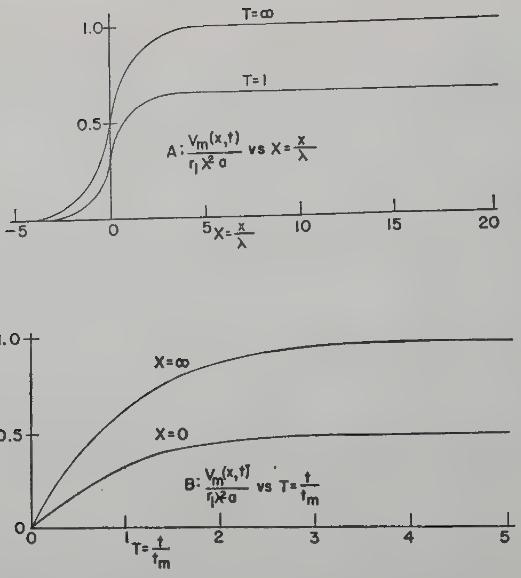

FIGURE 3. Membrane voltage (in addition to resting) graphed according to equation (31). In A, time, and in B, distance, is the parameter. Simple core conductor model with membrane of parallel resistance and capacity when current of the form $I(x) = 0$ for $x < 0$ and ax for $x > 0$ is suddenly applied. Curves are normalized to unity at t and x infinite.

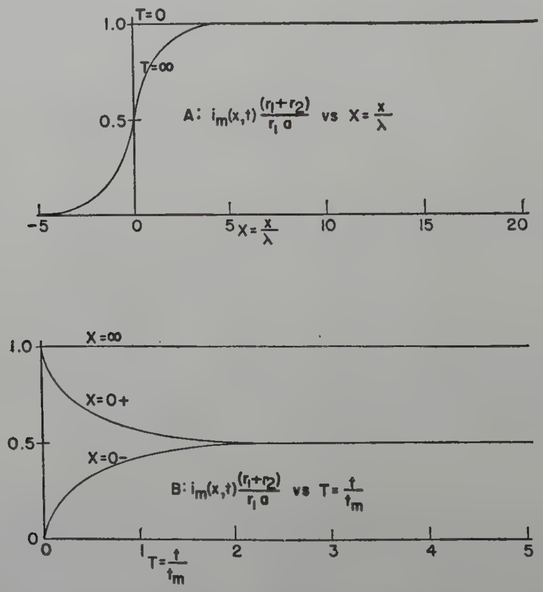

FIGURE 4. Membrane current graphed according to equation (32). Model and conditions as in Figure 3. $X = 0+$ and $X = 0-$ indicate values of membrane current as X approaches zero through positive and negative values respectively.

(32), and the solutions for applied longitudinal current in which a spatial step occurs (Hodgkin and Rushton, 1946; Davis, in Lorente de Nó, 1947).

Equations (31) and (32) are plotted in Figures 3 and 4 for certain values of X and T. In every graph, the equations have been normalized so that the coordinates are dimensionless. Figure 5 shows the initial and steady state core current under the same conditions, i.e., applied current of the form given by equation (20).

For the case actually used experimentally by the author (Taylor, 1950a, b) the normalized membrane current is shown in Figure 6. The conditions used to calculate this curve are those of Figure 1 and equation (19) where lambda is taken to be 0.3 cm., $x_0 = 17\lambda$, and $x_1 = 20\lambda$. Only the steady state is shown, but, as pointed out in the last section, the length of the plateau of membrane current is at its minimum in the steady state (cf. Fig. 4).

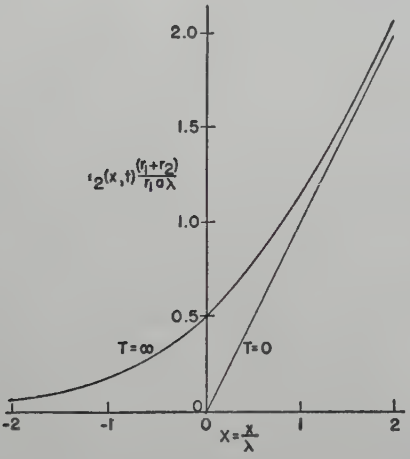

FIGURE 5. Core current according to equation (25) for steady state ($T = \infty$) and from integration of equation (32) for $T = 0$. Model and conditions as in Figure 3. Normalized to be dimensionless.

D. Nonlinear membrane impedance and some general remarks. Any nonlinear electrical properties of the nerve membrane would of course modify the above results. A nonlinear resistive component of the membrane impedance is undoubtedly present, as has been shown to be the case for nonmyelinated nerve (Cole and Curtis, 1940; Hodgkin, 1947; Hodgkin, Huxley, and Katz, 1949) and for muscle (Katz, 1948). A detailed analysis of the nonlinear case would be extremely difficult, even if the membrane properties of frog nerve were accurately known. It is reasonable to assume that the nonlinear voltage-current relation of the myelinated nodal membrane is similar to that of crab nerve or muscle, viz., resistance increasing slightly for applied anodal currents and decreasing considerably for applied cathodal currents. The effect of such a voltage-current relation on the curves plotted in Figures 3 to 6 would be to distort the spatial transient. For the case of applied cathodal currents this would be a favorable distortion, the reduced membrane resistance in the plateau region would decrease the space constant λ, sharpening the spatial transient and lengthening the plateau. The magnitude of the membrane current in the plateau region would not be altered.

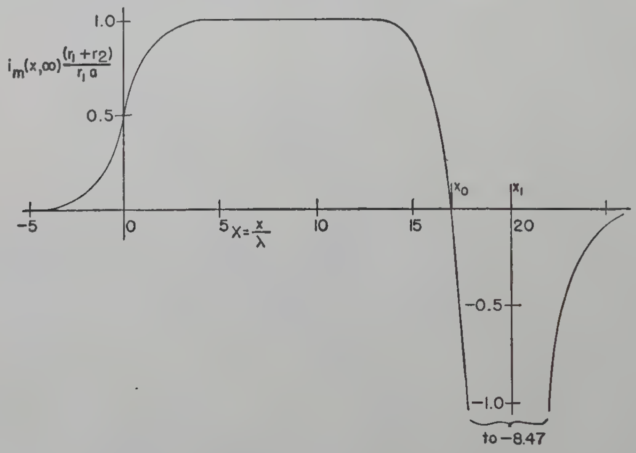

FIGURE 6. Normalized membrane current for the continuous core conductor model in the steady state under conditions approximately as used experimentally [see Figure 1 and equation (19)]. Lambda is assumed to be 0.3 cm. so that $x_0 = 17$ indicates that the triangular portion of the filter paper electrode was 5.1 cm. long. This graph was constructed by the superposition of curves from equation (32) and the known solution for membrane current in the vicinity of a unit step in applied longitudinal current (thin electrode at $x = x_1$).

Conversely, the distortion for anodal applied currents would broaden the spatial transient and shorten the plateau. The effect of large anodal currents on the membrane resistance of frog nerve is not known, but for the crab nerves studied by A. L. Hodgkin (1947) the resistance was quite linear up to applied anodal currents of six times threshold. If this were true for frog nerve, the effect would be negligible for anodal currents, while being desirable for cathodal.

There are some interesting relations of a general nature which help to clarify one's thinking in connection with the above analysis. Equation (3) is essentially one of two simultaneous partial differential equations in which the dependent variables are the membrane voltage V_m and current i_m, and the independent variables are time t and distance x. The relation between V_m and i_m in terms of the membrane electrical properties is the other simultaneous equation. It can be readily shown with the aid of the Fourier and Laplace transforms that if the second of these equations, expressing the impedance of the membrane, is a linear integral or differential equation in x alone, with constant coefficients but of any order, then one can make the following statement: Given the solution of equation (3) for some driving function (the collection of terms not involving the dependent variables, in this case $-r_1 i_p$), the solution for the case in which the driving function is the derivative with respect to x of the original one will be the derivative with respect to x of the original solution, at any time t. Now r_1 is a constant and i_p for the case of the usual bipolar method of applying current is the first derivative of the i_p for the case here considered. Thus the solutions for these two cases are related as a function and its first derivative with respect to x at any time t. Since it is clear that the membrane current in the mid-portion of the region between two widely separated narrow "polarizing" electrodes approaches zero, it is equally clear that a plateau should occur in the mid-portion of the region considered above.

Notice further that the membrane current is the first derivative of the core current. Thus the core current in the case of bipolar current application has the same form as the membrane current in the case of longitudinal linearly increasing applied current. Since it is obvious (or easily shown) that the core current in the mid-portion of the region between two thin electrodes will be almost independent of distance and of the membrane impedance, so must the membrane current be in this case.

PART II. THE DOUBLE CABLE MODEL

Since the results of these analyses were used in experimenting upon the sciatic-peroneal nerve of the frog, which is a large trunk surrounded by a dense and resistive connective tissue sheath, the effect of this sheath upon the current distribution has been considered. That this epineural sheath has a high resistance has been generally accepted for a long time (Bishop *et al.*, 1926) and has been pretty thoroughly demonstrated by C. Rashbass and W. A. H. Rushton (1949). The sheath was removed and its impedance measured by the author (1950b), and any doubt which remained concerning this point was effectively removed by F. Crescitelli (1951).

The term "double cable model" was introduced by Rashbass and Rushton who worked out several important relations. The assumptions involved are identical with those for the simple core conductor model treated above, with the addition of another concentric membrane, hereinafter called the "sheath," meant to represent the epineural sheath. A general integral will be derived which is applicable to any type of applied current, giving the steady state membrane and sheath current distributions. This integral will be explicitly solved for the case of a longitudinal linearly increasing applied current as above [Fig. 1 and equation (20)]. The geometry considered is shown in Figure 7.

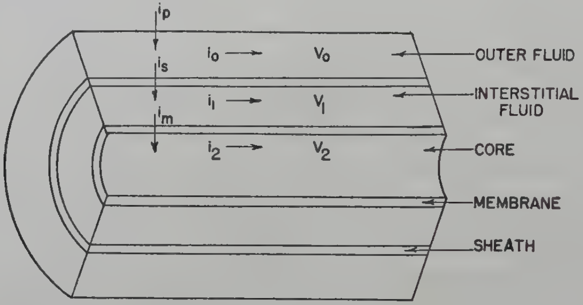

FIGURE 7. Geometry of double cable model considered. Section of infinitely long cylinder. For nomenclature see text.

The nomenclature is the same with the exception that:

$I = i_0 + i_1 + i_2$

$i_p = dI/dx$ is the current flowing radially into the outside fluid in amperes per cm

V_0 is the potential of the outer fluid in volts

r_0 is the resistance per centimeter of outside fluid

i_0 is the longitudinal current in the outside fluid in amperes

r_s is the resistance of one centimeter length of sheath in ohm cm

$V_s = V_1 - V_2$ is the potential across the sheath in volts

$$\lambda_s^2 = \frac{r_s}{r_0 + r_1}, \qquad \lambda_m^2 = \frac{r_m}{r_1 + r_2}$$

$$\frac{1}{\lambda_1^2} = \frac{1}{2}\left[\frac{1}{\lambda_s^2} + \frac{1}{\lambda_m^2} + \sqrt{\left(\frac{1}{\lambda_s^2} - \frac{1}{\lambda_m^2}\right)^2 - \frac{4r_1^2}{r_s r_m}}\right]$$

$$\frac{1}{\lambda_2^2} = \frac{1}{2}\left[\frac{1}{\lambda_s^2} + \frac{1}{\lambda_m^2} - \sqrt{\left(\frac{1}{\lambda_s^2} - \frac{1}{\lambda_m^2}\right)^2 - \frac{4r_1^2}{r_s r_m}}\right].$$

A. General integral steady state solution for any form of applied current. Using Ohm's and Kirchhoff's laws one writes down immediately

$$\frac{dV_j}{dx} = -r_1 i_j\,, \qquad (j = 0,\ 1,\ 2)$$

$$i_m = \frac{di_2}{dx}\,,$$

$$i_s - i_m = \frac{di_1}{dx}\,,$$

$$i_p - i_s = \frac{di_0}{dx}\,,$$

$$V_s = i_s r_s\,,$$

$$V_m = i_m r_m\,.$$

Differentiating $V_s = V_0 - V_1$ and $V_m = V_1 - V_2$ and substituting, we have

$$\frac{dV_s}{dx} = \frac{r_s di_s}{dx} = -r_0 i_0 + r_1 i_1\,,$$

$$\frac{dV_m}{dx} = \frac{r_m di_m}{dx} = -r_1 i_1 + r_2 i_2\,.$$

Differentiating again, solving for d^2i_s/dx^2 and d^2i_m/dx^2, substituting in λ_s^2 and λ_m^2 and rearranging, we have

$$\begin{aligned} \frac{d^2 i_s}{dx^2} &= \frac{i_s}{\lambda_s^2} - \frac{i_m r_1}{r_s} - \frac{i_p r_0}{r_s}\,, \\ \frac{d^2 i_m}{dx^2} &= \frac{-i_s r_1}{r_m} + \frac{i_m}{\lambda_m^2}\,. \end{aligned} \qquad (33)$$

Solving equations (33) by the use of the bilateral Fourier transform will allow the convenient use of the real convolution later. As before, the Fourier transform of i_m will be defined as

$$\bar{i}_m(m) = \int_{-\infty}^{\infty} i_m(x)\, e^{-mx}\, dx\,,$$

where m is the imaginary radian frequency $2\pi jf$; $j\sqrt{-1}$. Similarly, the Fourier transforms of $i_s(x)$ and $i_p(x)$ are $\bar{i}_s(m)$ and $\bar{i}_p(m)$ respectively.

Taking the Fourier transform of equations (33) yields

$$\begin{aligned} m^2 \bar{i}_s &= \frac{\bar{i}_s}{\lambda_s^2} - \frac{\bar{i}_m r_1}{r_s} - \frac{\bar{i}_p r_0}{r_s}\,, \\ m^2 \bar{i}_m &= \frac{-\bar{i}_s r_1}{r_m} + \frac{\bar{i}_m}{\lambda_m^2}\,, \end{aligned} \qquad (34)$$

and, solving these algebraically for $\bar{\imath}_s$ and $\bar{\imath}_m$, we have

$$\begin{aligned} \bar{\imath}_s(m) &= \frac{-\left(\frac{r_0}{r_s}\right)\left(\frac{m^2-1}{\lambda_m^2}\right)\bar{\imath}_p}{\left(\frac{m^2-1}{\lambda_s^2}\right)\left(\frac{m^2-1}{\lambda_m^2}\right)-\frac{r_1^2}{r_s r_m}}, \\ \bar{\imath}_m(m) &= \frac{\left(\frac{r_0 r_1}{r_s r_m}\right)\bar{\imath}_p}{\left(\frac{m^2-1}{\lambda_s^2}\right)\left(\frac{m^2-1}{\lambda_m^2}\right)-\frac{r_1^2}{r_s r_m}}. \end{aligned} \tag{35}$$

The zeros of the denominator are the expressions defined above as $1/\lambda_1^2$ and $1/\lambda_2^2$. The partial fraction expansions of equations (35) are readily obtained in terms of these expressions.

Introducing the following constants for convenience:

$$\begin{aligned} c_1 &= \frac{\frac{r_0}{r_s}}{2\left(\frac{1}{\lambda_2^2}-\frac{1}{\lambda_1^2}\right)}, \\ c_2 &= \left(\frac{1}{\lambda_1^2}-\frac{1}{\lambda_m^2}\right), \\ c_3 &= \left(\frac{1}{\lambda_m^2}-\frac{1}{\lambda_2^2}\right), \end{aligned} \tag{36}$$

all of which can be shown to be real and greater than zero for any possible combination of physical values of the parameters involved, the partial fraction expansion of (35) is

$$\begin{aligned} \bar{\imath}_s(m) &= 2\,c_1\left[\frac{-c_2}{\left(\frac{m^2-1}{\lambda_1^2}\right)}-\frac{c_3}{\left(\frac{m^2-1}{\lambda_2^2}\right)}\right]\bar{\imath}_p, \\ \bar{\imath}_m(m) &= \frac{2\,c_1 r_1}{r_m}\left[\frac{-1}{\left(\frac{m^2-1}{\lambda_1^2}\right)}-\frac{-1}{\left(\frac{m^2-1}{\lambda_2^2}\right)}\right]\bar{\imath}_p. \end{aligned} \tag{37}$$

For any given form of the applied current

$$i_p(x) = \frac{dI}{dx},$$

equations (37) express the Fourier transforms of the membrane and sheath current distributions. Equations (37) however are each the product of two transforms and one can apply the real convolution theorem to this case as was done above in the analysis of the simple core conductor model. The inverse Fourier transform of $\bar{\imath}_p(m)$ is by definition $i_p(x)$, and the inverses of the multipliers of $\bar{\imath}_p$ are quickly found with the information that the inverse of a transform of the form $k/(m^2 - D^2)$ is (Campbell and Foster, pair #444)

$$-\left(\frac{k}{2D}\right) e^{-D|x|},$$

provided only that D is real and greater than zero, which it is in every case under consideration.

Thus the inverses of equations (37) can be written down immediately as

$$\begin{aligned} i_s(x) &= c_1 \int_{-\infty}^{\infty} [\lambda_1 c_2 e^{-|x-z|/\lambda_1} - \lambda_2 c_3 e^{-|x-z|/\lambda_2}]\, i_p(z)\, dz\,, \\ i_m(x) &= \frac{c_1 r_1}{r_m} \int_{-\infty}^{\infty} [\lambda_1 e^{-|x-z|/\lambda_1} - \lambda_2 e^{-|x-z|/\lambda_2}]\, i_p(z)\, dz\,. \end{aligned} \qquad (38)$$

These are the integral expressions for the sheath and membrane current distributions for the double cable model for any type of applied current $i_p(x)$, so long as the Fourier transform of the expression for such current distribution exists. Equations (38) are readily integrated for any of the commonly encountered types of applied current.

B. Membrane current distribution in double cable model for longitudinal linearly increasing applied current. Integration of equations (38) for this case is very simple. Assuming an applied current of the form given by equation (20), i.e., $I = 0$ for x less than zero and $I = ax$ for x greater than zero, $i_p(x)$ is a unit step at the origin times a, the gradient of the applied current. The only part of the solution which will interest us here is the value of the membrane current for large values of x, since this will be the membrane current in the mid-polar region (cf. Fig. 1) if the total region is more than a few lambda long.

Integration of the second of the equations (38) under these conditions gives us

$$i_m(x) = \frac{a c_1 r_1}{r_m} [\lambda_1^2 (2 - e^{-x/\lambda_1}) - \lambda_2^2 (2 - e^{-x/\lambda_2})]\,. \qquad (39)$$

The plateau membrane current is $\lim_{x\to\infty} i_m(x)$ which is

$$i_m(\infty) = \frac{2 a c_1 r_1}{r_m} (\lambda_1^2 - \lambda_2^2)\,,$$

or, substituting the value of c_1 from (36),

$$i_m(\infty) = \frac{a r_0 r_1 \lambda_1^2 \lambda_2^2}{r_s r_m}.$$

However, from the definition of λ_1 and λ_2,

$$\lambda_1^2 \lambda_2^2 = \frac{r_s r_m}{(r_0 + r_1)(r_1 + r_2) - r_1^2},$$

and by substituting this and rearranging, the plateau membrane current is seen to be

$$i_m(\infty) = \frac{a}{1 + r_2\left(\frac{1}{r_1} + \frac{1}{r_0}\right)}. \tag{40}$$

Thus the plateau membrane current for the double cable model with longitudinal linearly increasing applied current does not depend upon the resistance of the membrane or of the sheath and is linearly related to a, the gradient of the applied current.

Integration of the first of the equations (38) is likewise not difficult, and it is readily shown that the sheath current in the plateau region is also independent of the membrane or sheath resistance.

Integration of the equations (38) for the usual type of bipolar current application is straightforward. The resultant form of the membrane current distribution has been shown by the author to fit the data of Rashbass and Rushton (1949) on frog nerve for the spread of excitability in the vicinity of a single pole very well (Taylor, 1950b). These curves also fit the data published by Lorente de Nó (1947) for the electrotonic spread in frog nerve and for the injury potential in the vicinity of a sharp cut. It follows therefore that these data of Lorente de Nó furnish no argument for the contention that longitudinal currents in the nerve core influence the distribution of membrane current in any except a purely passive, linear manner. No well authenticated data on frog nerve have been found by the author which do not fit the predictions of the double cable model theory. For an excellent discussion of some of these points the papers of Rashbass and Rushton should be consulted.

PART III. THE SALTATORY MODEL

A great deal of evidence has appeared to support the suggestion of R. S. Lillie (1925) that processes concerned with excitation and conduction in myelinated nerve occur at the nodes of Ranvier. At the present time no phenomena which are clearly in conflict with this view have been presented. In any event the resistance of the myelin sheath is so large in comparison to the resistance of the membrane at the nodes (Huxley and Stämpfli, 1949) that in a consideration of the effects of externally applied currents the assumption that the myelin is a perfect insulator is clearly justified.

The purpose of this section is to inquire into what effect this type of structure will have upon the distribution of membrane current when a longitudinal linearly increasing current is applied (Fig. 1).

The assumptions made here are identical with those for the simple core conductor model considered in the first part with the addition that the myelin is a perfect insulator, broken only at equally spaced interval by nodes of infinitesimal length and finite resistance (see Fig. 8). This model is identical with that considered by N. Rashevsky (1948) and Offner, Weinberg, and Young (1940) with reference to theories of conduction. Rashevsky's expression [1948, p. 133, eq. (17)] for the electrotonic spread ahead of the active region contains a space constant identical with that which is here derived.

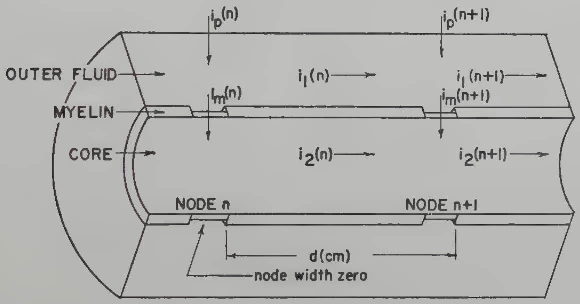

FIGURE 8. Geometry of saltatory model considered. Section of infinitely long cylinder. For nomenclature see text.

The nomenclature is the same as that used in the first part for the simple core conductor model except that the unit of length shall be "node" instead of centimeters. If the distance between nodes is designated by d, then $x = nd$ where n is the ordinal number of the nth node counting from the origin of x. Also, $i_1(n)$ and $i_2(n)$ are the currents flowing longitudinally between the node n and the node $n + 1$ in the external fluid and core respectively, r_m is the total resistance of any node, and r_1 and r_2 are the total resistances of external fluid and core between any two adjacent nodes. These relations are indicated in Figure 8.

Applying Ohm's and Kirchhoff's laws to this model, we have immediately

$$V_1(n) - V_1(n+1) = r_1 i_1(n), \tag{41}$$

$$V_2(n) - V_2(n+1) = r_2 i_2(n) \tag{42}$$

$$i_m(n) = i_2(n) - i_2(n-1), \tag{43}$$

and by definition

$$V_m(n) = V_1(n) - V_2(n), \tag{44}$$

$$I(n) = i_1(n) + i_2(n), \tag{45}$$

$$V_m(n) = i_m(n)\, r_m . \tag{46}$$

From (41), (42), and (44) we can write

$$V_m(n) - V_m(n+1) = r_1 i_1(n) - r_2 i_2(n),$$

and substitution of (45) gives us

$$V_m(n) - V_m(n+1) = r_1 I(n) - (r_1 + r_2)\, i_2(n). \tag{47}$$

Similarly:

$$V_m(n+1) - V_m(n+2) = r_1(n+1) - (r_1 + r_2)\, i_2(n+1). \tag{48}$$

Subtracting (48) from (47), substituting from (43) and (46) and introducing the constant

$$\phi = 1 + \frac{r_1 + r_2}{2 r_m}, \tag{49}$$

we find

$$i_m(n) - 2\phi i_m(n+1) + i_m(n+2) = \frac{r_1}{r_m}[I(n) - I(n+1)]. \tag{50}$$

This is the equation to be solved under the condition that a longitudinal linearly increasing current is applied, i.e.,

$$I(n+1) - I(n) - \begin{cases} 0, & n < 0, \\ a, & n \geqq 0. \end{cases} \tag{51}$$

The solution to equation (50) under the condition (51) has the form (Norlund, 1924)

$$i_m(n) = \begin{cases} c_1 e^{n w_1} + c_2 e^{n w_2}, & n < 0 \\ c_3 e^{n w_1} + c_4 e^{n w_2} + \dfrac{r_1 a}{r_1 + r_2}, & n \geqslant 0, \end{cases} \tag{52}$$

where e^{w_1} and e^{w_2} are the roots of the equation

$$y^2 - 2\phi y + 1 = 0, \tag{53}$$

and c_1, c_2, c_3, and c_4 are constants.

Solving equation (53) gives the roots as

$$e^{w_1} = \phi + \sqrt{\phi^2 - 1}\,,$$

$$e^{w_2} = \phi - \sqrt{\phi^2 - 1} = e^{-w_1}\,,$$

so the solution (52) can be written

$$i_m(n) = \begin{cases} c_1 e^{nw_1} + c_2 e^{-nw_1}\,, & n < 0 \\ c_3 e^{nw_1} + c_4 e^{-nw_1} + \dfrac{r_1 a}{r_1 + r_2}\,, & n \geqslant 0\,. \end{cases} \tag{54}$$

Before proceeding to evaluate the constants in equation (54) two theorems will be presented.

Definition: A system S will be said to obey the principle of superposition with respect to a variable s under the conditions that: If the driving forces $f_1(s)$, $f_2(s)$, and $f_3(s)$ produce the results $r_1(s)$, $r_2(s)$, and $r_3(s)$ respectively, then for any f_1 and f_2 such that $f_1 + f_2 = f_3$, it is also true that $r_1 + r_2 = r_3$.

Theorem 1: In any system which obeys the principle of superposition with respect to the variable s, if $f(s)$ produces $r(s)$ and if $f(s)$ is an odd function of s, $r(s)$ is also an odd function of s.

Proof: We can immediately write down the following:

$$f(s) \text{ produces } r(s)\,,$$
$$-f(-s) \text{ produces } r(s)\,,$$
$$f(-s) \text{ produces } r(-s)\,.$$

Adding the first and third:

$$f(s) + f(-s) \text{ produces } r(s) + r(-s)\,.$$

Subtracting the second from the first:

$$f(s) + f(-s) \text{ produces zero}\,.$$

Clearly then, $r(s) + r(-s) = 0$.

Theorem 2: In any system which obeys the principle of superposition with respect to the variable s, if $f(s)$ produces $r(s)$ and $f(s)$ is independent of s, $r(s)$ is also independent of s.

Proof: The proof of this theorem follows directly when it is shown that if $f(s)$ produces $r(s)$, then $df(s)/ds$ produces $dr(s)/ds$, provided the derivatives exist. The truth of the latter is immediately obvious if the derivatives are written out in terms of their fundamental definitions.

We can now return to equation (54). Application of the above two theorems tells us that the solution $i_m(n)$ has the property that $i_m(n) - i_m(0)$ is an odd function of n. This is true because if the quantity $ar_1/2r_m$ were added to the driving function of equation (51) it would then be an odd function of n. But then the solution would be an odd function of n and would differ from the solution of (51) by not more than an additive constant. Since from physical considerations we have the boundary condition that, as n becomes large negatively, i_m must approach zero, clearly i_m must be bounded for large positive n. Thus $c_2 = c_3 = 0$ in equation (54). After setting these equal to zero the bound for positive n is seen to be $r_1a/(r_1 + r_2)$ and the above-mentioned additive constant must be just one-half of this and it must be equal to the value of $i_m(0)$.

Therefore

$$c_1 = \frac{r_1 a}{2\,(r_1 + r_2)}$$

and from the second part of (54)

$$i_m(0) = c_4 + \frac{r_1 a}{r_1 + r_2} = \frac{r_1 a}{2\,(r_1 + r_2)}\,.$$

Thus

$$c_4 = \frac{-\,r_1 a}{2\,(r_1 + r_2)}$$

and (54) can be written

$$i_m(n) = \begin{cases} \dfrac{r_1 a}{2\,(r_1 + r_2)}\, e^{nw_1}\,, & n \leqslant 0\,, \\[2ex] \dfrac{r_1 a}{2\,(r_1 + r_2)}\,[2 - e^{-nw_1}]\,, & n \geqslant 0\,. \end{cases} \tag{55}$$

If the quantity $1/w_1$ is formally identified with lambda for the simple core conductor model, the form of the membrane current in the two cases is the same [cf. limit of (22) times p as p approaches zero], and all of the general conclusions apply to both. Thus the myelinated structure does not interfere with the plateau which is predicted for the mid-polar region when a linearly increasing longitudinal current is applied, with the direct relationship between the membrane current density in this region and the gradient of the applied current, nor with the fact that the membrane current in this region is independent of the membrane resistance.

The relation between the lambda for the simple model and $1/w_1$, however, is not simple and direct. It is easily shown that

$$w_1 = \cosh^{-1}\left[1 + \frac{r_1 + r_2}{2\,r_m}\right],$$

while

$$\lambda = \sqrt{\frac{r_m}{r_1 + r_2}}\,,$$

where the quantities in the latter case refer to one centimeter length of nerve and in the former to the distance between nodes. These relations tell us that the membrane at a node does not have the same effect on membrane current spread as the same resistance spread out over the distance *d* between nodes, and that measurements made on myelinated nerve and interpreted in terms of the simple model will lead to results which are consistent, but not to the correct values of longitudinal resistances or of the resistance at nodes (e.g., Lorente de Nó, 1947, pp. 479 ff.).

SUMMARY

It has been shown that if a steady longitudinal current which increases linearly with distance along the nerve is applied to any of the passive models considered a plateau occurs in the curve of membrane current versus distance (or node number). The value of the membrane current in the plateau region is not dependent upon the properties of the membrane as long as they are linear, and is directly proportional to the longitudinal current gradient.

For the simple core conductor model with membrane composed of resistance and capacity in parallel the complete solution for a suddenly applied current of this kind has been presented. It is seen that in this case the region over which the membrane current is plateau-like is greatest immediately following the application of current and least in the steady state. From the general integral solution it was pointed out that this is the case as long as the membrane is such that its current voltage characteristics are like those in any equivalent linear network containing no inductance. It is clear that this conclusion holds for the double cable model and the saltatory model as well. Thus the steady state analysis gives the minimum distance over which a plateau in the membrane current would be expected to occur.

It was pointed out that in the plateau region of membrane current, the core current is increasing linearly, with distance and that experimental results strongly indicate that it is the transverse membrane current which modifies the properties of the nerve and not at all the longitudinal current in the core.

Reference was made to experiments by the author that tend to bear out the applicability of these results to myelinated fibers of frog nerve with intact epineural sheath, viz., conduction velocity is altered, by applied currents of this type, equally throughout the region of the expected plateau.

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